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The Western Journal of Medicine

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ARTICLES

10 Delayed Bottle Weaning and Iron Deficiency in Southeast Asian Toddlers
E GRAHAM, T CARLSON, K SODERGREN, J DETTER, and R LABBE

15 Current and Future NIH Support of Biomedical Research
C LENFANT

19 Motor Vehicle Crashes and Maternal Mortality in New Mexico: The Significance of Seat Belt Use
M SCHIFF, L ALBERS, and P McFEELEY

CONFERENCES AND REVIEWS

23 Hepatitis G Virus: Is It a Hepatitis Virus?
R CHEUNG, E KEEFFE, and H GREENBERG

EPITOMES

34 Important Advances in Pathology

ALERTS, NOTICES, AND CASE REPORTS

40 AIDS-Related Lymphomas With Neurologic Manifestations
C SWEENEY and W AGGER

44 Wegener Granulomatosis Causing Sellar Mass, Hydrocephalus, and Global Pituitary Failure
R BERTKEN and V COOPER

47 An Anterior Mediastinal Mass With Draining Sinus Due to Nocardia braziliensis
D M KROE, N SHULMAN, C KIRSCH, and J WEHNER

EDITORIAL

50 The Alphabet Soup of Viral Hepatitis: Is G a New Flavi(or) in the Mix?
H BONKOVSKY

CORRESPONDENCE

52 Onychomycosis—A Different Perspective • Response • Corrections

LESSONS FROM THE PRACTICE

54 The Final Act
C DERK

OTHER FEATURES

2 Subscription Information

5 Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming

49 Poem

55 Classified Advertising

58 Instructions for Authors

Detailed Table of Contents: 3, 4

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CONTENTS

ARTICLES

10 **Delayed Bottle Weaning and Iron Deficiency in Southeast Asian Toddlers**

ELINOR A. GRAHAM, MD, MPh; TIMOTHY H. CARLSON, PhD, RD; KATHERINE K. SODERGREN, RN; JAMES C. DETTER, MD; and ROBERT F. LABBE, PhD

From the Departments of Pediatrics and Laboratory Medicine, Harborview Medical Center, University of Washington, Seattle, Washington.

15 **Current and Future NIH Support of Biomedical Research**

CLAUDE LENFANT, MD

From the National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland.

19 **Motor Vehicle Crashes and Maternal Mortality in New Mexico: The Significance of Seat Belt Use**

MELISSA SCHIFF, MD; LEAH ALBERS, CNM, DrPH; and PATRICIA McFEELEY, MD

From the Department of Obstetrics and Gynecology, College of Nursing, and the Department of Pathology, Office of the Medical Investigator, University of New Mexico Health Sciences Center, Albuquerque, New Mexico.

CONFERENCES AND REVIEWS

23 **Hepatitis G Virus: Is It a Hepatitis Virus?**

RAMSEY C. CHEUNG, MD; EMMET B. KEEFFE, MD; and HARRY B. GREENBERG, MD

From the Division of Gastroenterology, Department of Medicine, Stanford University School of Medicine, Stanford, California, and the VA Palo Alto Health Care System, Palo Alto, California.

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Pathology

Items of progress in pathology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance.

34 **Laboratory Work-Up of Patients With Heritable Thrombotic Disorders**

RICHARD NEWMAN, MD

35 **Determining the Number of Copies of HIV-1 RNA in Plasma: Applying This New Test to Management of Patients**

LUIS M. DE LA MAZA, MD, PhD

36 **Laboratory Detection of *Chlamydia trachomatis***

ELLENA M. PETERSON, PhD

36 **Diseases Associated With the Major Histocompatibility Complex**

STEVEN R. SLOAN, MD, PhD

37 **Kaposi's Sarcoma-Associated Herpesvirus (KSHV): A New Viral Pathogen Associated With Kaposi's Sarcoma, Primary Effusion Lymphoma, and Multicentric Castleman's Disease**

JONATHAN SAID, MD

38 **Cocaethylene: A Novel Cocaine Homolog**

DAVID N. BAILEY, MD

ALERTS, NOTICES, AND CASE REPORTS

40 **AIDS-Related Lymphomas With Neurologic Manifestations**
CHRISTOPHER J. SWEENEY, MB, BS, and WILLIAM A. AGGER, MD
From the Division of Medical Education and the Section of Infectious Disease, Gunderson Clinic, LaCrosse, Wisconsin.

44 **Wegener Granulomatosis Causing Sellar Mass, Hydrocephalus, and Global Pituitary Failure**
RICHARD D. BERTKEN, MD, and VIRAF R. COOPER, MD
From the Departments of Rheumatology and Neurosurgery, University Medical Center of Fresno, University of California San Francisco, Fresno, California.

47 **An Anterior Mediastinal Mass With Draining Sternal Sinus Tracts Due to *Nocardia braziliensis***
D. MARK KROE, MD; NANCY SHULMAN, MD; CARL M. KIRSCH, MD; and JOHN H. WEHNER, MD
From the Departments of Pulmonary and Critical Care Medicine and Infectious Diseases, Stanford University School of Medicine, Stanford, California, and the Division of Respiratory and Critical Care Medicine, Santa Clara Valley Medical Center, San Jose, California.

EDITORIAL

50 **The Alphabet Soup of Viral Hepatitis: Is G a New Flavi(or) in the Mix?**
HERBERT L. BONKOVSKY, MD
From the Division of Digestive Disease and Nutrition, University of Massachusetts Medical Center, Worcester, Massachusetts.

CORRESPONDENCE

52 **Onychomycosis—A Different Perspective**
ERNST EPSTEIN, MD
ADITYA K. GUPTA, MD; RICHARD K. SCHER, MD; PIET De DONCKER, PhD; DANIEL N. SAUDER, MD; and NEIL H. SHEAR MD Respond

53 **Corrections**

LESSONS FROM THE PRACTICE

54 **The Final Act**
CHRIS DERK, MD

OTHER FEATURES

2 WJM Subscription Information
5 Continuing Medical Education Activities
49 Poem
55 Classified Advertising
58 Instructions for Authors

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

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ALLERGY

January 18–23, 1998—**36th Annual Scientific Session of The Western Society of Allergy and Immunology.** Four Seasons Resort, Wailea in Maui, Hawaii. For more information contact Rebecca Gough, Exec. Administrator, PO Box 1122, Roanoke, Texas, 76262; (817) 491-2616, Fax (817) 491-2241).

ANESTHESIOLOGY

November 14–16—**9th Annual Anesthesiology Update, 1997.** UC Davis at Monterey Plaza Hotel. Fri.–Sun. Contact: (916) 734-5390.

CARDIOLOGY

August 1–3—**Cardiology in Primary Care.** San Diego. Sponsored by Continuing Medical Education Associates. Hotel del Coronado, San Diego. Method: AV, L, SB, W. $495. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

August 7–9—**Critical Care in Cardiology.** American College of Cardiology at Palace Hotel, San Francisco. Thurs.–Sat. 16.5 hrs. Contact: Registration Secretary, Extramural Programs Dept. ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814-1699. (800) 253-4636, ext. 695.

October 16–18—**21st Annual Cardiology Update 1997.** American College of Cardiology at Carmel Valley Ranch Resort. Thurs.–Sat. 12 hrs. Contact: ACC Registration Secretary, Extramural Programs Dept. ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814-1699. (800) 253-4636, ext. 695.

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September 27–28—**The Skin From A to Z.** UCSF at Laurel Heights Campus, UCSF. Sat.–Sun. 10 hrs. $275. Contact: UCSF.

EMERGENCY MEDICINE

August 19–20—**High Risk Emergency Medicine.** Sponsored by National ACEP & Emergency Physicians' Medical Group. Tues.–Wed. Mission Valley Hilton, San Diego. 15 hrs. $299-499. Contact: Nations Executive Travel (800) 651-CEME.

October 17–19—**Essentials in Emergency Medicine and Urgent Care.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency La Jolla, San Diego. Method, AV, L, SB, W. $495. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

November 10–14—**Emergency Medicine Symposium II.** UCSD at La Jolla Marriott. Mon.–Fri. 32 hrs. $495. Contact: UCSD (619) 534-3940.

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August 1–3—**Cardiology in Primary Care.** Continuing Education Associates at San Diego Hotel Del Coronado. Fri.–Sun. 20 hrs. $495. Contact: CMEA, PO Box 270469, San Diego, 92198-2469, (800) 993-CMEA.

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August 18–22—**Essentials of Primary Care: A Core Curriculum for Practice in the Managed Care Era.** UCSF at Squaw Creek Resort, N. Lake Tahoe. Mon.–Fri. 25 hrs. $625. Contact: UCSF.

August 22–24—**Primary Care Medicine: A Practical Approach.** Scripps Clinic at Le Meridien San Diego at Coronado, San Diego. Fri.–Sun. 16 hrs. Contact: Laurel Steigerwald, Dept. Academic Affairs 403-C. Scripps Clinic, 10666 N. Torrey Pines Rd., La Jolla 92037. (619) 554-8556.

September 25–27—**HIV, AID & Women.** OCME at La Jolla Marriott, San Diego. Thurs.–Sat. 14 hrs. $175. Contact: OCME (619) 534-3940.

September 27–30—**OB/GYN Review.** USC at Red Lion Hotel, Glendale. Sun.–Tues. 38 hrs. Contact: USC.

September 27—**2nd Annual Women's Health Symposium.** UCD at Davis Medical Center, Sacramento. Sat. Contact: UCD.

GERIATRICS

September 4–6—**Sports Medicine for the Mature Athlete.** OCME at Sheraton Grande Torrey Pines, La Jolla. Thurs.–Sat. Contact: OCME (619) 534-3940.

November 10–12—**Geriatrics Update, 1997.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $475. Mon.–Wed. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

INFECTIOUS DISEASE

September 25–27—**HIV, AID & Women.** OCME at La Jolla Marriott, San Diego. Thurs.–Sat. 14 hrs. $175. Contact: OCME (619) 534-3940.

November 7–9—**Advances in Infectious Disease.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort,

San Diego. Method: AV, L, SB, W. $475. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

INTERNAL MEDICINE

August 17–20—**New Advances in Internal Medicine.** UCD at Embassy Suites, Monterey. Sun.–Fri. Contact: UCD.

August 22–24—**Primary Care Medicine: A Practical Approach.** Scripps Clinic at Le Meridien San Diego at Coronado, San Diego. Fri.–Sun. 16 hrs. Contact: Laurel Steigerwald, Dept. Academic Affairs 403-C. Scripps Clinic, 10666 N. Torrey Pines Rd., La Jolla 92037. (619) 554-8556.

September 26–30—**Internal Medicine 1997—Fall Program.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $675. Fri.–Tues. 30 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

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October 16–17—**Neuroradiology Update.** Thu.–Fri. Hotel Del Coronado, Coronado, California. $300. Sponsored by UC San Diego. Information: Ryals & Associates, Inc., PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773; Fax: (770) 552-9859; http://www.ryalsmeet.com.

October 20–22—**Neurology and Outpatient Psychiatry in Primary Care.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency La Jolla, San Diego. Method: AV, L, SB, W. $495. Mon.–Wed. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

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September 13—**2nd Annual Cancer Research Program.** UCD at Sierra Health Foundation, Sacramento. Fri. 6 hrs. $95. Contact: UCD.

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September 25–27—**The Fetus & Newborn: State-of-the-Art Care.** Contemporary Forums at Hotel del Coronado, San Diego. Thurs.–Sat. 16 hrs. $415. Contact: Contemporary Forums, 11900 Silvergate Drive, Dept. 348, Dublin, CA, 94568. (510) 828-7100, ext. 0.

October 25–28—**Pediatric Facial Plastic Surgery.** UCD at Monterey Plaza Hotel. Sat.–Tues. Contact: UCD.

PSYCHIATRY

November 14–16—**43rd Annual Group Therapy Symposium.** UCSF at Mark Hopkins Hotel, San Francisco. Fri.–Sun. 20 hrs. $340. Contact: UCSF.

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October 18—**New Treatment Advances for Psychosis.** UCD at UC Davis Medical Center, Sacramento. Sat. Contact: UCD.

RADIOLOGY

August 31–September 4—**Neuroradiology Review; Including the Head, Neck and Spine.** Sun.–Thu. The Four Seasons Hotel, Newport Beach, California. $725. Sponsored by UC Irvine. Information: Ryals & Associates, Inc., PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773; Fax: (770) 552-9859; http://www.ryalsmeet.com.

September 20–21—**Ultrasound Update: 1997.** UCD at DoubleTree Hotel, Sacramento. Sat.–Sun. Contact: UCD.

October 16–17—**Neuroradiology Update.** Thu.–Fri. Hotel Del Coronado, Coronado, California. $300. Sponsored by UC San Diego. Information: Ryals & Associates, Inc., PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773; Fax: (770) 552-9859; http://www.ryalsmeet.com.

October 18–19—**17th Annual Comprehensive Review of Vascular & Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat.–Sun. 14.5 hrs. $325. Contact: Ryals & Assoc. (770) 641-9773.

October 20–24—**Multispecialty Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon.–Fri. Contact: Ryals & Assoc. (770) 641-9773.

October 22–26—**Musculoskeletal MR.** Wed.–Sun. The Westin Resort Hotel, Hilton Head, SC. $550. Sponsored by UC San Diego. Information: Ryals & Associates, Inc., PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773; Fax: (770) 552-9859; http://www.ryalsmeet.com.

SURGERY

September 5–7—**Surgery: Science Advancing the Art.** UC Irvine at La Quinta Desert Springs Resort (Palm Springs). Fri.–Sun. 7 hrs. $250. Contact: Medical Student Conference Committee c/o Medical Education. UC Irvine, School of Medicine, P.O. Box 4089, Irvine 92717-4089.

September 19–20—**3rd Annual Surgical Review: Update in Minimally Invasive Surgery, Trauma and Ultrasound.** UCD at David Grant Medical Center, Fairfield. Fri.–Sat. Contact: UCD.

October 4–5—**New Directions in Lasers & Cosmetic Surgical Procedures: A Hands-On Course.** UCD at UC Davis Medical Center, Sacramento. Sat.–Sun. Contact: UCD.

GENERAL/MULTIDISCIPLINARY

August 16–17—**ACLS Provider.** AHA at San Leandro. Sat.–Sun. 16 hrs. $170. Contact: CPR Seminars (510) 632-6135.

August 26—**ACLS Instructor Renewal.** AHA at Concord. Tues. $100. Contact: Rozann (510) 754-7900 or Alice (510) 828-1563.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Lorna Linda University, Continuing Medical Education Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education, (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

September 4—**ACLS Renewal.** AHA at Fremont. 6 hrs. Thurs. $100. Contact: Rozann (510) 754-7900 or Alice (510) 828-1563.

September 18–21—**8th Annual Conference of The American Academy of Pain Management.** Alexis Park Hotel & Spa, Las Vegas, Nevada. Contact: AAPM, (209) 533-9744; Email: aapm@aapainmanage.org; Website: www.aapainmanage.org.

September 29 & October 6—**ACLS Instructor Course.** AHA at Concord. 10 hrs. Mon. $195. Contact: Rozann (510) 754-7900 or Alice (510) 828-1563.

October 3—**Pre-ACLS Study Workshop.** AHA at San Leandro. Fri. 7.5 hrs. $50–$70. Contact: CPR Seminars (510) 632-6135.

October 24—**ACLS Renewal.** AHA at San Francisco. Fri. 6 hrs. $100. Contact: CPR Seminars (510) 632-6135.

October 25–26—**ACLS Provider.** AHA at San Francisco. Fri. 16 hrs. $170. Contact: CPR Seminars (510) 632-6135.

October 23–26—**Nevada Academy of Family Physicians 9th Annual CME/Golf Meeting.** The Orleans Hotel & Casino, Las Vegas. 19 hrs. Contact: Barbara Bolling, NAFP, PO Box 27713, Las Vegas, NV 89126-1713. (702) 228-5822.

January 28–31, 1998—**Medicine Meets Virtual Reality:6. Art, Science, Technology: Healthcare (R)Evolution.** San Diego Hyatt Regency. Wed.–Sat. Contact: AMA, Inc. (760) 741-8841.

February 13–16, 1998—**California Academy of Family Physicians 50th Annual Scientific Assembly.** Anaheim Hilton and Towers. $275–$385. 26+ hrs. Contact: Clark W. Franklin, California Academy of Family Physicians, 114 Sansome St., Suite 1305, San Francisco, CA 94104-3824. (415) 394-9121; fax (415) 394-9119; Email: cfranklin@familydocs.org.

HOME STUDY/SELF-ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

The listing of continuing medical education programs in Idaho is compiled by the Ada County Medical Society. To list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701. (208) 336-2930.

Brochures, course information, and registration forms are available from the contact person or organization.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

August 1–2—**26th Annual Santa Fe Cardiology Symposium.** Hilton of Santa Fe. Fri.-Sat. Contact Jim Hendricks or Renee Ketcham, Southwest Cardiology Associates, 1101 Medical Arts Ave., Bldg. 3, Albuquerque, NM 87102. (505) 247-4815, fax (505) 247-4356.

August 16—**Update in Primary Care (NMHMA).** Saturday. Albuquerque. Contact: Kelly Little, (505) 828-0237.

September 12–13—**American College of Surgeons Scientific Program.** Albuquerque. Fri.-Sat. Contact: Kelly Little, (505) 828-0237.

September 22–26—**MMI Healthcare Risk Management Certificate Program (HRMCP).** Albuquerque Marriott Hotel. Mon.-Fri. Contact: Gail Harris, (505) 883-0266.

January 23–24, 1998—**28th Annual Winter Pediatric Orthopaedic Seminar.** Albuquerque. Fri.-Wed. Contact: UNM Continuing Medical Education, Campus Box 713, Albuquerque, NM 87131-5126. (505) 272-3942, fax (505) 272-8604.

SATELLITE COURSES

Immunization Update 1997
September 17

Hepatitis C
Sometime in November

Contact: Joe Treat, Immunization Program, (505) 827-2366

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt

Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UANS:	Utah Association of Neurological Surgeons, 24 S 1100 East, Ste 302, Salt Lake City 84102. (801) 531-7806.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

OTHER CME OPPORTUNITIES

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. November 14–16—**Scottsdale Headache Symposium**. Scottsdale at Marriott's Camelback Inn Resort & Spa. Contact: (609) 845-1720.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. January 16–18, 1998—**Headache Now/Cancun**. The Ritz-Carlton, Cancun, Mexico. Contact: (609) 845-1720

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. June 26–28, 1998—**Fortieth Annual Scientific Meeting of The American Association for the Study of Headache.** Sheraton Palace, San Francisco. Contact: (609) 845-1720

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. November 6–8, 1998—**Scottsdale Headache Symposium.** Scottsdale at Marriott's Camelback Inn Resort & Spa. Contact: (609) 845-1720..

AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE. October 26–30—**49th Annual State-of-the-Art Conference.** Opryland Hotel, Nashville, Tennessee. Sun.–Thur. Contact: ACOEM, 55 W. Seegers Rd., Arlington Heights, Ill 60005. (847) 228-6850, ext. 184, FAX (847) 228-1856; Website: www.acoem.org.

Arrhythmias: Interpretation, Diagnosis & Management. *July 11–13*, Hyatt Regency, Lake Tahoe, NV. *October 31–November 1*, Le Meridien, San Diego. *December 12–14*, Monte Carlo Hotel, Las Vegas, NV. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

The Atopy Syndrome in the Third Millenium. *October 2–3, 1998*, Zurich, Switzerland, on the occasion of the 50th anniversary of the allergy unit at the Dept of Dermatology, University Hospital, Zurich, and in collaboration with the European Academy of Allergology and Clinical Immunology. Contact: Prof. Dr. B. Wüthrich, Zurich, 41-1-255-3079, fax 41-1-255-4431.

Clinical Endocrinology for Primary Care Physicians. *September 26–28*, Crowne Plaza Hotel, San Francisco, CA. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

Coronary Heart Disease Update. *August 22–24*, Hyatt regency, Monterey, CA. *November 21–23*, Monte Carlo Hotel, Las Vegas, NV. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731

Dermatology for the Non-Dermatologist. *September 26–28*, Monte Carlo Hotel, Las Vegas, NV. *November 21–23*, Disneyland Pacific Hotel, Anaheim, CA. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

CONTINUING MEDICAL EDUCATION

Managing Respiratory Diseases. *August 8–10*, Tenaya Lodge, Yosemite, CA. *October 31–November 2*, The Phoenician Resort, Scottsdale, AZ. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

Neurology for the Non-Neurologist. *August 8–10*, Snowmass Lodge, Aspen, CO. *October 24–26*, Monte Carlo Hotel, Las Vegas, NV. *December 12–14*, Camelback Inn, Scottsdale, AZ. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

UNIVERSITY OF NEBRASKA. August 27—**Breastfeeding: Baby's Natural Choice Conference**. Omaha. Wed. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. September 12—**Cancer Care for the 2st Century**. Omaha. Fri. $30. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. September 22–27—**Skills and Knowledge for the Practicing Physician**. Omaha. Mon.–Sat. $750. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. October 6–8—**5th International Symposium "Blood Cell Transplantation."** Omaha. Mon.–Wed. $350. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. October 10—**5th Annual College of Medicine Alumni Day**. Omaha. Fri. Free. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. December 11–13—**Obstetrics & Gynecology Conference**. Bally's, Las Vegas, NV. Thu.-Sat. $325. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha NE 68198-5651. (800) 642-1095.

NOTICE

State Associations should send their CME listings for publication to:

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Western Journal of Medicine
1224 W Main St, Ste 200
Charlottesville, VA 22903-2858

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Articles

Delayed Bottle Weaning and Iron Deficiency in Southeast Asian Toddlers

ELINOR A. GRAHAM, MD, MPh; TIMOTHY H. CARLSON, PhD, RD; KATHERINE K. SODERGREN, RN; JAMES C. DETTER, MD; *and* ROBERT F. LABBE, PhD, *Seattle, Washington*

We undertook this study to determine if culturally influenced feeding practices are associated with iron deficiency in infants and toddlers from low-income families. We obtained a dietary survey, illness history, hematocrit, and zinc protoporphyrin–to-heme ratio (ZPP/H) from 35 Southeast Asian children and 73 children of other ethnicities between ages 5 and 30 months. We confirmed iron deficiency by serum ferritin measurement in children with ZPP/H >80 mmol/mol or evaluated them after a 3-month iron treatment. Sixty percent of the Southeast Asian children had elevated ZPP/H ratios, compared with 14% of children of other ethnicities. Follow-up studies confirmed iron deficiency in 12 of 21 Southeast Asian children with elevated ZPP/H; 75% (eight) of those with confirmed iron deficiency were 24 to 30 months of age. We found that toddler feeding practices differ between Southeast Asians and other ethnic groups. All 17 Southeast Asian toddlers were still bottle fed at their second birthday, compared with 10 of 21 same-age children of other ethnicities. Persistence of bottle feeding after 2 years of age was highly associated with elevation of ZPP/H in Southeast Asian children but not in other children. Clinicians need to be aware of this problem and carefully monitor iron status in children not weaned from the baby bottle by age 2 years. Changes in education practices and policies are needed to prevent iron deficiency from the overintake of cow's milk that results from prolonged bottle feedings in this ethnic group.

(Graham EA, Carlson TH, Sodergren KK, Detter JC, Labbe RF. Delayed bottle weaning and iron deficiency in southeast asian toddlers. West J Med 1997 July; 167:10-14)

With the increased use in the US of iron supplements with breastfeeding and iron-fortified formulas, the prevalence of iron deficiency in children younger than 1 year has decreased.[1,2] Because of its impact on the psychomotor development of children, however, iron deficiency does remain a significant concern.[3,4] In Seattle's Harborview Medical Center, an urban clinic in a city with a large Southeast Asian immigrant population, we have seen many Southeast Asian toddlers with severe iron-deficiency anemia. The following case illustrates the problem.

> A 27-month-old Southeast Asian child, whose caregiver complained of poor solid food intake for 3 months, was brought in with pallor and stomachaches. The child was consuming large amounts of whole milk from a baby bottle. Physical examination was normal except for marked pallor. Hematocrit was 15%, Hb 3.8 g/dL, MCV <50 fL; blood smear showed marked microcytosis and hypochromia; zinc protoporphyrin–to-heme ratio (ZPP/H) was 454 mmol/mol (normal ≤80 μmol/mol); and G6PD screen was negative. Chart review showed normal hemoglobin electrophoresis. At 14 months of age, soon after being changed from an iron fortified formula to whole milk, the hematocrit had been 34% and the ZPP/H ratio 53 mmol/mol. After 2 months of oral iron therapy and decreasing the whole milk intake to 8 ounces a day, the child's hematocrit returned to 33%.

Cases such as this led us to conduct a screening study among a multiethnic population of young children to determine the incidence of iron deficiency in different ethnic groups (Carlson TH, Graham EA, unpublished data, 1997). The investigation in this current report was conducted to determine if culturally influenced feeding practices were associated with the high prevalence of iron deficiency in Southeast Asian toddlers found in the first study.

ZPP/H was the index used since it detects altered iron metabolism at an early stage of iron deficiency before

From the Departments of Pediatrics (Drs Graham and Sodergren) and Laboratory Medicine (Drs Carlson, Detter, and Labbe), Harborview Medical Center, University of Washington, Seattle, Washington.

This work was supported in part by National Institutes of Health grant no. DK35816.

Reprint requests to Elinor A. Graham, MD, Department of Pediatrics, Harborview Medical Center, Box 359774, 325 Ninth Ave, Seattle, WA 98104.

ABBREVIATIONS USED IN TEXT

ZPP/H = zinc protoporphyrin–to-heme ratio
WIC = Special Supplemental Food Program for Women, Infants and Children

anemia appears and can be done on the small amount of blood cells left over after the hematocrit determination.[5] Protoporphyrin normally combines with either iron or zinc in erythropoiesis to produce heme or zinc protoporphyrin. If iron availability is limited, the level of zinc protoporphyrin increases.

Methods

The study subjects (Table 1) consisted of 108 children between the ages of 5 and 30 months, seen consecutively at their regular visits to the WIC Program (Special Supplemental Food Program for Women, Infants and Children) during a 5-month period between October 1991 and March 1992. Information obtained included age, sex, ethnicity, length of enrollment in WIC, feeding practices during the first year of life, history of febrile illness lasting >24 hours in the previous week, and treatment with oral iron in the previous 3 months. In addition, for toddlers (≥2 years of age), parents were asked if weaning from the baby bottle had occurred at the time of the visit, and if so, at what age. Charts of all children with elevated ZPP/H were reviewed for number of illness visits in the 3 months before the WIC visit and prior hematologic evaluation or iron treatment. The study was approved by the University of Washington Human Subjects Review Committee.

All families met the low-income guidelines to qualify for the WIC program. Thirty-five children were first- or second-generation Southeast Asians, primarily from Laos and Cambodia, and 73 children were classified as "other," including 29 African and African-American, 18 European-American, eight Hispanic, and 18 mixed-ethnicity children.

Centrifuged micro-hematocrits were determined from capillary blood samples according to WIC program requirements. The same specimens were subjected to ZPP/H ratio analysis using the ProtoFluor-Z hematofluorometry system (Helena Laboratories, Beaumont, TX).[6] Children treated with iron as the result of an abnormal ZPP/H ratio (>80 μmol/mol) had hemoglobin, hematocrit, and red blood cell indexes determined by Coulter analysis. When possible, serum ferritin concentration (Stratus Fluorometic System, Baxter Healthcare, Miami, FL) was determined before iron treatment. After 3 months of oral iron treatment (5–6 mg elemental iron/kg body weight per day), Coulter analyses and ZPP/H tests were repeated.

All laboratory tests were monitored by an internal quality control program and by proficiency testing programs administered by the College of American Pathologists or other recognized proficiency testing programs. To avoid interference from bilirubin or other contaminants, specimens with ZPP/H >80 μmol/mol underwent a repeat ZPP/H analysis on washed red blood cells. The repeat measurement was reported as the final ZPP/H level.

Data were analyzed using the RS/1 statistical package (BBN Software Products, Cambridge, MA) or StatView II (Abacus Concepts, Berkeley, CA). The two-tailed Student's t test was used to compare the mean ZPP/H levels of Southeast Asian children and children of other ethnicities. The nonparametric Mann-Whitney test was used to compare mean ZPP/H by age groups and by weaning status in 2-year-old children.

Results

Southeast Asian children had a mean ZPP/H that was significantly higher than the mean for children of other ethnicities (108 vs 65 μmol/mol; $P < 0.0001$), but mean hematocrit values for Southeast Asian children were slightly higher than those of the other children (35 ± 3% vs 34 ± 2%; $P < 0.01$). Two-thirds of the children with ZPP/H >80 μmol/mol were Southeast Asian, as were 10 of the 11 children with ZPP/H >120 μmol/mol. Overall,

TABLE 1.—*Characteristics of Study Children, Ages 5–30 Months, Seen in WIC Clinic for Routine Nutrition Assessment and Hematocrits*

	Total (n = 108)	*Southeast Asian (n = 35)*	*Other* (n = 73)*
Age (years)	1.4 ± 0.8	1.7 ± 0.8	1.3 ± 0.7
Months enrolled in WIC	15 ± 10	20 ± 10	13 ± 8
Fraction of life in WIC	0.9 ± 0.2	1.0 ± 0.1	0.8 ± 0.3
Sex (male/female)	60/48	20/15	40/33
Infection in past week	23 (21)	2 (6)	21 (29)
Iron treatment in past 3 months	12 (11)	2 (6)	10 (14)
Type of infant feeding in first year			
Iron-fortified formula	79 (73)	29 (83)	50 (69)
Breastfeeding and formula	25 (23)	4 (11)	21 (29)
Other	4 (4)	2 (6)	2 (3)

Data are means ± SD or *n* (%).
*Including 29 African-American, 18 European-American, eight Hispanic, and 18 mixed-race children.

60% of the Southeast Asian children had elevated ZPP/H vs 14% of all other children.

Southeast Asian children had higher mean ZPP/H at all age levels. In contrast to children of other ethnicities, they showed an increase in ZPP/H from infancy through toddler age. The differences in ZPP/H by age among other children were not significant (Figure 1). Twelve of the 17 Southeast Asian toddlers ≥2 years of age had elevated ZPP/H, and this age group made up 57% of all of the Southeast Asian children with elevated ZPP/H. In contrast, only two of the 21 non-Asian 2-year-old toddlers had elevated ZPP/H.

Although similar percentages of Southeast Asian and other children were given iron-fortified formula up to 1 year of age (Table 1), the Southeast Asian children were much more likely to be bottle fed with cow's milk as 2-year-olds. Less than half (10 of 21) of the other children were bottle fed at 2 years of age and only six were still bottle fed at the time of their WIC visit and blood test. All 17 of the Southeast Asian toddlers ≥2 years of age were still bottle fed at their second birthday and only four had been weaned from the bottle at the time that their blood was sampled. Bottle feeding continued in spite of strong recommendations by WIC staff to wean by 18 months of age. Persistence of bottle feeding after 2 years of age in Southeast Asian children was highly associated with elevation of ZPP/H (Figure 2). Bottle feeding was not associated with increased mean ZPP/H in the non-Asian children of this age group.

Quantity of cow's milk consumed appeared to be related to the association of prolonged bottle feeding and elevated ZPP/H in Southeast Asian toddlers. Dietary surveys in the records of our sample indicated that some toddlers consumed relatively large amounts of cow's milk, in some cases 1.4 L/day, twice the WIC recommended amount for children this age. In addition, they had low intake of solid foods with significant iron content.

Further evidence suggesting that iron deficiency was a major cause of the elevated ZPP/H values of the Southeast Asian children, especially for the toddler-age group, was provided by complete follow-up studies in 15 children. Six of the 21 children with elevated ZPP/H did not return for follow-up studies (or their studies were incomplete). Twelve of the 15 children with complete follow-up had additional studies indicating iron deficiency, including seven children with pretreatment ferritin levels <12 mg/L; four children with a >10 mg/L (>1 mg/dL) increase in hemoglobin and a >20% decrease in ZPP/H after 3 months of iron treatment; and one child with a 21% decrease in ZPP/H after 3 months of treatment (normal ZPP/H posttreatment) but no change in the initial normal hematocrit. Nine of the 12 with confirmed iron deficiency were ≥24 months of age. Three children were either iron replete based on normal ferritin levels before treatment or showed no response in ZPP/H or hemoglobin concentration after >3 months of iron treatment.

Other causes of elevated zinc protoporphyrin were considered. Lead poisoning, an alternative cause of high ZPP/H, is virtually unknown among children in the Seattle area. Three of the four children with ZPP/H >200 μmol/mol were tested, and all lead levels were <0.39 μmol/L (8 μg/dL). Recurrent febrile illness has also been associated with elevated ZPP/H.[7] Only one Southeast Asian child with elevated ZPP/H was reported to have had a febrile illness in the prior week. Seven of the 21 Southeast Asian children with elevated ZPP/H had a clinic visit for illness in the preceding 3 months, but only one was seen more than once. In contrast, nine of the 10 children of other ethnicities with elevated ZPP/H were seen for illness in the prior 3 months and five were seen two or more times. Parents reported illness in the week prior to blood testing in six of these 10 children.

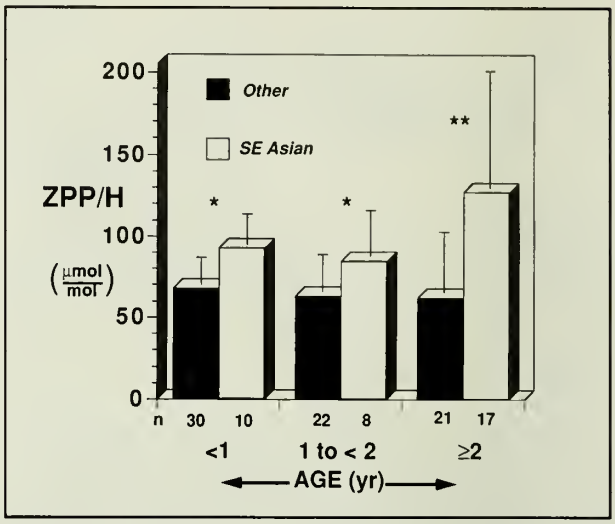

Figure 1.—Effect of age on ZPP/H in children under 3 years of age by ethnic backgrounds. Mean ZPP/H levels in all age groups were higher in Southeast Asian children compared to those of other ethnic backgrounds but was markedly higher for the ≥2 year-old group. * indicates $P<0.05$; ** indicates $P< 0.001$. The number of children in each group is indicated by n. The error bars represent one standard deviation.

Discussion

The high prevalence of elevated ZPP/H ratios and iron deficiency in Southeast Asian toddlers in our sample has been observed in other studies in the past decade, although prevalence was not as high as in our sample. These studies did not look at the feeding practices of the children with elevated ZPP/H. A Minnesota household survey found that 22.8% of US-born low-income Southeast Asian children (mean age 1.9 years) had elevated ZPP/H. The majority of those children with elevated ZPP/H had serum ferritin levels <15 mg/L.[8] A study of Asian children 6 to 36 months of age in Montreal found a higher prevalence of iron deficiency in toddlers—16.5% of 19–36-month-old children were iron deficient compared with 11.4% of 6–12-month-old and 9.9% of 13–18-month-old children.[9] In contrast, a cross-sectional sample of US children[10] and a longitudinal study of French Canadian children found decreasing iron deficiency in children 2 years and older.[11]

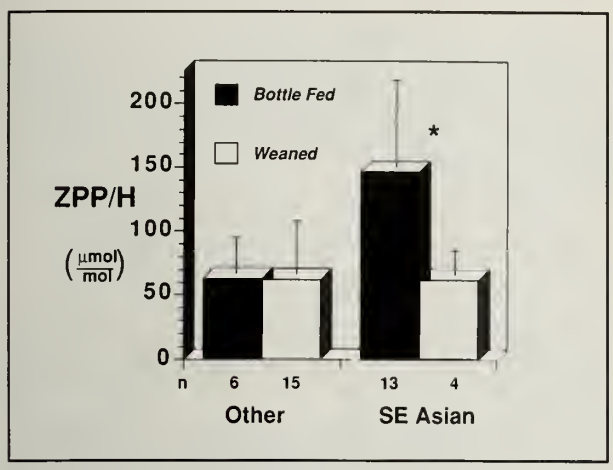

Figure 2.—Influence of weaning on ZPP/H in 2-year-old Southeast Asian children compared to same age children of other ethnic backgrounds. At the time of blood sampling, bottle-fed Southeast Asian children had significantly higher mean ZPP/H levels than bottle-weaned Southeast Asian toddlers. No difference was noted in the mean ZPP/H by type of feeding in children of other ethnicities. *$P<0.01$. The error bars represent one standard deviation.

From a review of literature and discussions with WIC staff and clinic interpreters, we consider several factors to contribute to the prolonged bottle feeding and excess cow's milk intake in this ethnic group. In Southeast Asia, children are normally breastfed until 2 years of age or until they are displaced from the breast by a new baby. Early weaning from either breast or bottle is not a cultural practice. Studies in the United States and other countries have documented the decline in breastfeeding among Southeast Asian immigrants.[12–15] Bottle feeding is substituted for breastfeeding and is often continued until 3 or 4 years of age. Southeast Asian children are started on semisolid or solid foods much later than is the practice of other ethnic groups.[16] Families often live in crowded households and place a priority on keeping infants and toddlers from crying or disturbing others. Children are given a bottle when they cry,[17] and it is easier for a toddler to consume large amounts of milk from a bottle than a cup, as use of a cup requires adult supervision. Southeast Asian parenting practices generally put an emphasis on accommodation to infants; gradual change is the rule, so rapid bottle or breast weaning is not culturally acceptable.[15] Finally, the provision of free cow's milk by the WIC program and the lack of iron-containing food selections, except iron-fortified cereals, may encourage the practice of feeding large amounts of milk to toddlers. Unfortunately, culturally acceptable nourishing foods such as rice, noodles, tofu, vegetables, and familiar meats are not provided through the WIC program.

The iron deficiency noted in Southeast Asian toddlers in our study generally had not progressed to anemia at the time of sampling. These children may not be at risk for adverse psychomotor effects if they are weaned from the bottle before anemia develops. Most studies of iron deficiency and child development, however, have involved children <24 months of age. It is possible that iron deficiency without anemia may have adverse effects on development in children 2 to 3 years of age if it persists for long periods of time without detection and intervention.

The retrospective design of this study is a significant limitation. Although quantity of milk intake was often noted, it was not consistently present in the records. Therefore it was not possible to quantitate cow's milk intake or iron content of solid foods consumed. A quantitative dietary history, obtained prospectively, could provide more detail of cultural differences in infant feeding practices. It is likely that iron deficiency results from the quantity of milk consumed. Similarly, prospectively obtaining venous blood samples on all children at the time of the WIC visit would have provided more precise determination of iron status.

Since conducting this study, we have found that hemoglobinopathies including hemoglobin E, alpha and beta thalassemia trait, are associated with a mild increase in mean ZPP/H in iron-sufficient adults.[18] Such disorders are common in Southeast Asians, with prevalence as high as 40 to 60%.[19] This may explain the findings in our sample of higher mean ZPP/H at all ages in Southeast Asian children compared with those of other ethnicities. This type of population factor, however, would not explain the associations of increased ZPP/H with age and with persistent bottle feeding after age 2 years in Southeast Asian children in our sample.

An important outcome of this study is the demonstration that if hematocrit had been used as the only screening test for iron status, a large fraction of the iron-deficient Southeast Asian children would not have been identified. The ZPP/H, a very sensitive screening test for iron deficiency, provided information about iron status that correlated well with dietary histories. It identified children at risk to develop anemia and allowed for timely and appropriate nutritional intervention.

Conclusions and Implications for Pediatric Practice

1. Cultural influences that prolong bottle feeding past 2 years of age are associated with iron deficiency in Southeast Asian toddlers. Weaning to a cup with increased solid food intake should be encouraged by 18 months of age. Where this is not accomplished, toddlers should be monitored for development of iron deficiency, and oral iron supplements should be provided.

2. The pattern of prolonged bottle feeding in Southeast Asian families does not appear to change in response to current health education approaches encouraging early weaning. Since many of these children are in the WIC program, development of culturally sensitive education approaches and materials by WIC could help encourage earlier weaning. Culturally acceptable food supplement packages for children >1 year of age—providing high-protein foods besides dairy products and foods with substantial amounts of iron and vitamin C (to aid iron absorption)—would also encourage a more

nutritionally adequate diet for these toddlers. Iron fortification of toddler foods should be considered to prevent iron deficiency in spite of prolonged bottle feeding.[20]

3. Hematocrit is not a sensitive screening test for iron status, especially in the Southeast Asian toddler population because of its high risk for dietary iron deficiency. It is recommended that programs such as WIC use ZPP/H as an inexpensive screening test for iron deficiency in the toddler population.

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Current and Future NIH Support of Biomedical Research

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This article is based on a lecture given at the Western Association of Physicians Conference held in Carmel, California, in February 1997.

Current and future prospects for biomedical research are discussed by examining two critical questions, namely, how much money will be available and how it will be spent. Context is provided first by comparing how those same questions were answered 25 years ago with what has actually occurred between 1972 and the present. The questions are then addressed for a comparable period in the future. Projections are made for future funding for the National Institutes of Health (NIH) and examples of new research directions are described. Ample grounds are provided for optimism about the future of biomedical research and NIH funding for it.

(Lenfant C. Current and future NIH support of biomedical research. West J Med 1997 July; 167:15-18)

I should tell you that the title was not of my choosing. It was Dr. Mason's. In his letter of invitation, he said, "I believe the audience would be most interested in your views on current and future NIH support of Biomedical Research." When I read that sentence, I knew immediately what he was talking about. Over the years that I have been Director of the National Heart, Lung and Blood Institute (NHLBI), I have heard many variants of the same question, but it always comes down to one thing: money—exactly how much of it are we going to have?

It is an interesting coincidence that the last time I was in Carmel was 25 years ago. Although I had only been with the NIH and away from academia for a year, I was invited to come here to do basically the same thing I am doing today. Now, however, I am in the position of being able to give you my perception of where we are and where we are going on the basis of what I have seen during the last 25 years. One thing I have learned over that time is that Edmund Burke knew what he was talking about two hundred years ago when he said, "You can never plan the future by the past" (Letter to the National Assembly, 1791).

As I was deciding what I would share with you I thought it would be appropriate to remind myself of the predictions I made 25 years ago. I would like to take you through those predictions to see how good they were—it may give you some indication of how good my predictions for the next 25 years are going to be. In 1972, I asked two questions: "How much money will be available?" and "How will it be spent?" Taking the "How much" question first, I reconstructed what I did then by looking at the NIH budget over the preceding 25 years (Figure 1). Since an extrapolation based on the entire period seemed inappropriate given the rapid increase over the early years, I instead projected 25 years ahead, based on the annual rate of increase over the 10 previous years. As may be seen from Figure 1, it was not such a bad projection actually. The NIH budget increased at an annual rate of more than 9 percent for the past 25 years.

Now for the second question—"How was the money spent?" Here, it is instructive to compare what actually happened over the past 25 years with what I spoke about in 1972. During the hearings on the NHLBI budget for 1973, Ted Cooper, who was then Director of the Institute, discussed cholesterol testing, heart disease, and the impact of "high blood fats." Mr. Flood, the Chairman of the House Appropriations Subcommittee, said to Dr. Cooper, "Are you hearing about recent rumblings to the contrary that fat may not be so bad after all?" It is difficult to read a statement like that and not think to yourself, "Nothing has really changed over the last 25 years." And yet we know that, indeed, much has changed since then. About 10 years after Dr. Cooper's testimony, some very significant papers were published that established a clear relationship between cholesterol and coronary heart disease.[1,2]

Dr. Cooper made another notable prediction in 1972—one concerning the "hemophilic fraction." Specifically, he said that "... for the hemophilic fraction, which has been isolated and studied in detail, it may be possible to produce this agent from nonhuman sources.... Bovine and porcine sources are two possible ones." If we consider

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ABBREVIATIONS USED IN TEXT
NIH = National Institutes of Health
NHLBI = National Heart, Lung and Blood Institute

that factor IX was recently produced for the first time by recombinant DNA techniques, I think we can safely say that this prediction of 25 years ago has been realized—even if not quite in the way that was expected.

One of the major public health successes over the last 25 years, the National High Blood Pressure Education Program, was initiated in 1972. It was created to determine whether awareness and control of high blood pressure in this country could be increased and the associated health burden thereby reduced. Surveys conducted periodically since the program's inception have shown conclusively that the answer is yes—for women and for men and for blacks and for whites. This certainly qualifies as another successful 1972 prediction.

On the other hand, one thing that was not predicted very well in 1972 is the important role of molecular biology and molecular genetics in the research we are doing today. In fact, it appears that many questioned the possibility that gene transplantation would ever have any particular value. In an article published in *Science* a number of years ago, it was noted that Dr. French Anderson had submitted a paper titled "Current Potential for Modification of Genetic Defects" to the *New England Journal of Medicine* in 1968.[3] It was rejected as "too speculative" and "medical prediction." Apparently, some of the reviewers were not so skilled at prediction themselves, considering that just a few years ago the first paper on the use of gene therapy was published, with French Anderson as one of its authors.[4] Today, I believe it is fair to say that gene therapy is on the verge of being a successful therapy for a number of conditions.

So, despite the oversight of molecular medicine, a number of important successes were foreseen. Overall, the years 1972 to 1997 were quite successful, with very significant scientific achievements being enabled by relatively generous financial support.

And that brings us to our main subject, namely, what will happen between now and 2022. So now let us look to the next 25 years. The overarching question is, "Will they be good, bad, or indifferent?" Of course, I have no way of knowing for sure, but I do have an opinion, and I would like to relate it to you in the context of those same two questions I explored previously, namely, "How much money will be available?" and "How will it be spent?"

Again addressing the money question first, I would like to explain a little bit about the recent history of the NIH budget, and I will start with an article by Drs. Bishop, Kirschner, and Varmus. The article, titled "Science and the Administration," appeared in *Science* early in 1993 before Dr. Varmus became the Director of the NIH.[5] "Until a full evaluation has been completed," the authors wrote, "we recommend increasing the NIH budget by 15% per year, which would double the budget in current dollars by 1998."

When just a few months later Dr. Varmus had settled into his new position, he quickly realized that things at the NIH were not quite the way they might be envisioned from a university setting. As he himself said in a lecture in late 1993, "Our first proposal was arresting—by some accounts self-serving and naive—because we elected to give a number, albeit tentative, to annual increases for the NIH budget."[6] He went on to say, "The five-year caps on discretionary spending, the large obligations to entitlements, the national paranoia about tax increments, and the gaping hole of the national debt are more than enough to restrain growth of the entire

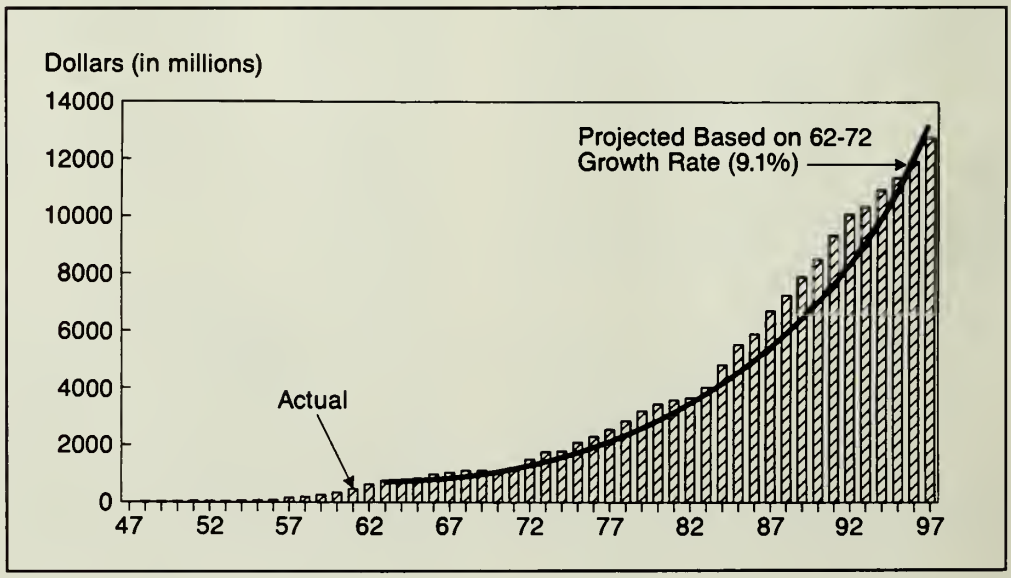

Figure 1.—Actual NIH obligations, fiscal years 1947–1997 and projected NIH obligations, fiscal years 1972–1997, based on actual NIH obligations, fiscal years 1962–1972.

research enterprise, including NIH. To overcome hurdles of this sort, we will need a cell biologist to run the Office of Management and Budget, not just NIH. In the meantime we will be fortunate to stay ahead of inflation in the next few years." As it turns out, the post-appointment Harold Varmus was a much better predictor of what actually happened.

But there is still more to the story. In 1995, two years after he arrived at the NIH, Dr. Varmus was invited to give the Shattuck Lecture in Boston, where he made two significant points.[7] One was the need to recognize that the research enterprise was "undergoing a painful transition from an era of growth to an era of steady-state activity," and the other was that "many of the initiatives recently proposed or undertaken at the NIH ... are designed to cope with the steady state." These statements were clearly inconsistent with doubling the NIH budget in five years. And yet, the reason he stressed those points in 1995 was that some discussions were already taking place in Washington on the issue of money and on what the 1996 NIH budget was likely to be. With the change in the leadership in Congress, everyone was talking about reducing the deficit, and the balanced budget amendment was very much in the forefront.

Although the President's budget proposed to increase the NIH budget for 1996, that increase was to be followed by steady reductions through the year 2000, at which time the NIH budget would be only slightly greater in current dollars than it was in 1993. A proposal from the new leadership of the House of Representatives was even more discouraging. It envisioned an immediate decrease of 5% for 1996, followed by level funding through the year 2000. Yet even that scenario was optimistic compared to a proposal from the Senate, which included a nearly 10% decrease for 1996 and level funding thereafter through 2000.

None of these approaches factored in what Mr. John Porter, the Chairman of the House Appropriations Subcommittee on Labor, Health and Human Services—the one before which we testify—had in mind. He made it very clear that he wanted to increase the NIH budget, and increase it he did. The 1996 NIH budget was 5.7% above the 1995 budget and the 1997 figure was another 6.9% above that.

The logical next question is, can he continue to do it? Well, Mr. Porter is quite shrewd and a very good politician and, to help ensure continued strong support for the NIH, he did something quite remarkable. He brought in the "Nobel-ity," i.e., a group of Nobel Prize winners in biomedicine to address the issue of "Is what the NIH doing worth it?" In particular, are there some important things ahead of us that will justify increased appropriations for the NIH?

Here are some of the statements made at that 1995 hearing.[8] "For the first time in my 30 years as a scientist and for the first time in a public setting, I say that I now believe we will eventually conquer cancer." That was Michael Bishop. Michael Brown made this statement, "I believe that atherosclerosis will one day be a disease of the past, like polio and smallpox."

I should note that a year after his appearance before Mr. Porter's committee, Michael Brown co-authored with Joe Goldstein an editorial in *Science* titled, "Heart Attack: Gone with the Century?"[9] It included this sentence: "Exploitation of recent breakthroughs—proof of the cholesterol hypothesis, discovery of effective drugs, and better definition of genetic susceptibility factors—may well end coronary disease as a major public health problem early in the next century." I have to say, from a personal perspective, that I hope they are correct, because it would at least somewhat justify the problems that editorial has caused me. As you all know, the views of Drs Brown and Goldstein carry a lot of weight. Many people, having read the editorial, have said, "Heart disease is no longer a problem—why don't you do research on something else instead?" The answer, of course, is that heart disease remains a very big problem, and there is every reason to believe that it will continue to be one for the foreseeable future. According to a recent report by researchers at the Harvard School of Public Health for the World Health Organization, titled "The Global Burden of Disease," ischemic heart disease, which ranked fifth on the global disease burden list in 1990, is expected to top the list in 2020.[10]

And that again brings us to our second question, namely, "How will the money be spent?" I think that there are in front of us extraordinary opportunities. It is the primary reason for my optimism about the future of the NIH. I have selected a few exciting examples of current work in our area, but keep in mind that similar ones could be provided for each of the other institutes of the NIH. Certainly, one of the most important recent developments is an expansion of interest in genetic influences on disease. Just consider how far we have come—a 1973 report prepared for the NHLBI included the following statement: "Recent studies have shown genetic influence on the metabolism of lipoproteins, on the excretion of sterol, and on the atherogenetic reaction of the arterial wall."[11] Now, about a quarter century later, we have reached the point where an article can be published in a scientific journal that asks the question, "Can Genes Prevent Atherosclerosis?"[12] Moreover, I think that today most knowledgeable people would be inclined to say probably yes—perhaps not in all cases, but certainly in many cases. Another example of truly exciting work reported last year is the preliminary success of Isner and his colleagues in Boston using gene therapy to bypass arterial blockage.

Let me also note some recently published work on the impact of "modifier genes." The importance of further advances in this area is indicated by key statements from two such papers. One asserts that "susceptibility to a complication of hypertension is under, at least partially, independent genetic control from susceptibility to hypertension itself."[13] The other reports "the existence of primary, blood pressure–independent, genetic factors predisposing to a complex form of stroke."[14] This kind of

ABBREVIATIONS USED IN TEXT

OMI = Office of the Medical Investigator

For this investigation, we explored the OMI database for all pregnancy-associated deaths from 1986 through 1995. Of 97 identified, 47 were injury-related, 33 involving motor vehicle crashes. We reviewed the OMI autopsy reports, police crash scene reports, and other relevant records of these 33 fatalities for decedent's age, ethnicity, fetal gestational age, time of death, rural vs urban location of crash, type of road (highway or nonhighway), seat belt use, and drug and alcohol use. Ethnicity was coded from the death certificate. Time of crash was defined as day (8 a.m. to 3:59 p.m.), evening (4 p.m. to 11:59 p.m.), or night (midnight to 7:59 a.m.). Fetal gestational age was estimated using history and autopsy evaluation of the fetus. Alcohol involved in the crash was defined as the presence of alcohol in the decedent or in others involved in the crash.

We present descriptive statistics and compare proportions across the variables of interest, with differences assessed by χ^2 test. Statistical analysis was performed utilizing the SAS statistical package.[11]

We also calculated a rate of pregnancy-associated motor vehicle fatalities per 100,000 woman-years of pregnancy in New Mexico for 1986 through 1995. The numerator—the number of pregnancy-associated deaths from motor vehicle crashes—was derived from the OMI data. The denominator—the total number of live births, fetal deaths (defined as death of a fetus from any cause between 20 weeks and term), and abortions—was reported by the New Mexico Bureau of Vital Records and Health Statistics. Because pregnancy duration is less than one calendar year, we adjusted the denominator to account for woman-years of exposure. We made several assumptions: average length of pregnancy is 38 weeks post-ovulation, average gestation at abortion is 12 weeks, and average gestation at fetal death is 30 weeks. We adjusted live births by multiplying the number of live births by 44 (weeks of pregnancy plus 6 weeks postpartum) and dividing by 52 (weeks per year). We adjusted abortions and fetal deaths similarly, multiplying the number of abortions by 18 and dividing by 52 and multiplying the number of fetal deaths by 36 and dividing by 52.

We compared the above rate with the average number of motor vehicle fatalities among nonpregnant women ages 15–44 years (subtracting the motor vehicle deaths during pregnancy) per 100,000 nonpregnant women ages 15–44. For the denominator, we used the mean number of women ages 15–44 for 1986 through 1994 and subtracted the number of pregnant women during those years (as estimated by the mean number of live births, fetal deaths, and abortions adjusted for woman-years of exposure for 1986 through 1994).

Results

From 1986 through 1995, the New Mexico Office of the Medical Investigator reported 97 pregnancy-associated deaths. Of these, 50 were from medical complications and 47 were from injury (Figure 1). Motor vehicle crashes accounted for 33 (~70%) of the 47 injury-related deaths. A high proportion of decedents were in the last trimester of pregnancy (Table 1); one was postpartum. The New Mexico population is made up of 50% non-Hispanic whites, 37% Hispanics, and 9% American Indians; minorities—Hispanic and American Indian women—were overrepresented among the crash deaths. Few decedents had positive blood levels of illicit drugs (6%) or alcohol (9%) at the time of death (Table 1).

Table 2 describes crash data for the pregnancy-associated deaths. The majority of deaths were among women passengers on rural highways throughout New Mexico. The collisions were equally divided between single and multiple vehicle crashes (data not shown). The majority of decedents (77%) were not wearing seat belts at the time of the crash. A woman killed in a crash in a rural area was significantly less likely to be wearing a seat belt compared with a woman killed in an urban area ($P < 0.003$) (data not shown). Most of the crashes (79%) occurred during the evening or nighttime hours, and 45% of the crashes involved alcohol. Alcohol was significantly more likely to be involved in nonhighway crashes than in highway crashes ($P < 0.002$) (data not shown).

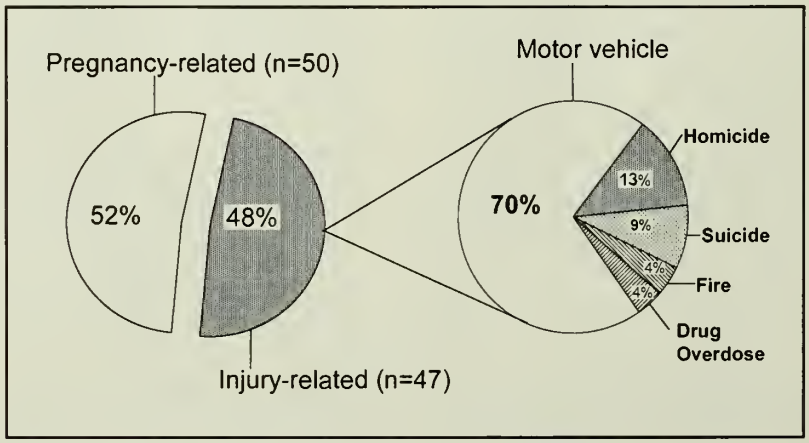

Figure 1.—Pregnancy-associated deaths in New Mexico, 1986 through 1995.

TABLE 1.—*Demographics of Pregnancy-Associated Motor Vehicle Deaths (n=33)*

	Number	Percent
Age (years)		
16–19	6	18
20–29	24	73
30–34	3	9
Gestational age		
First trimester	6	18
Second trimester	11	33
Third trimester	14	41
Postpartum	1	4
Unknown	1	4
Ethnicity		
Non-Hispanic white	10	30
Hispanic	15	46
American Indian	7	21
Other	1	3
Drug use by decedent		
Yes	2	6
No	18	54
Unknown	13	40
Alcohol use by decedent		
Yes	3	9
No	28	85
Unknown	2	6

TABLE 2.—*Comparison of Motor Vehicle Crash Deaths, Pregnancy-Associated vs New Mexico Population*

	Pregnancy-Associated Motor Vehicle Deaths 1986–1995		New Mexico Population Deaths 1990* (percent)	P
	Number	Percent		
Occupancy				
Driver	10	30	44	0.06
Passenger	20	61	40	
Pedestrian	3	9	16	
Time of crash				
Day	7	21	25	NS
Evening	17	52	44	
Night	9	27	31	
Location of crash				
Urban	10	30	31	NS
Rural	23	70	69	
Type of road				
Highway	23	70	17	<0.001
Nonhighway	10	30	83	
Seat belt use**				
Yes	5	17	21	NS
No	23	77	79	
Unknown	2	6	—	
Alcohol involved in crash				
Yes	15	45	60	NS
No	13	39	40	
Unknown	5	16	—	

*From New Mexico Traffic Safety Bureau Report.[12]
**n = 30 (excludes three pedestrian deaths).

Table 2 also compares the pregnancy-associated crash fatalities with all New Mexico crash fatalities for 1990, the middle year of our study period. Time and location of crash, vehicle occupancy, seat belt use, and alcohol-related crashes were similar for pregnant vs nonpregnant victims. More pregnancy-associated motor vehicle fatalities occurred on highways vs nonhighways.

Using the calculations noted in Methods, we compared the rate of pregnant and postpartum women killed in motor vehicle crashes (13.1/100,000 women) to the rate of nonpregnant women ages 15–44 killed in motor vehicle crashes (21.5/100,000 women) during the 10-year time period.

Discussion

Injury-related deaths account for a significant proportion of fatalities among pregnant women. Dannenberg et al.[5] reported that among pregnancy-associated injury deaths in New York City, 63% were homicides, and significantly more homicides of pregnant black women were observed than expected. Varner and Rubin et al. reported that motor vehicle fatalities account for 4 to 71% of all pregnancy-associated injury deaths in the US.[7,13] Our study is the first to provide details about fatal motor vehicle crashes among pregnant women.

The study has several limitations. Ascertainment of all pregnancy-associated deaths from injuries may be incomplete because medical investigators may not have recognized some deaths in recently pregnant (less than 6 weeks) or postpartum women. This limitation may be compounded by the retrospective design of this study. Finally, the small number of deaths in our study limits the conclusions that can be drawn.

In 1994, New Mexico ranked third in the US for motor vehicle fatality rates.[9] Pregnant and postpartum women are not excluded from this cause of death—from 1986 through 1995 in New Mexico, nearly half of all pregnancy-associated deaths were due to injury, and the majority of those were caused by motor vehicle crashes. Pregnant women do account for fewer motor vehicle fatalities than nonpregnant, reproductive age women in New Mexico, as is clear from the difference in fatality rates (13.1 vs 21.5 per 100,000 women). We surmise that women may be less likely to participate in risk-taking behaviors (such as drug and alcohol use) during pregnancy than nonpregnant women of reproductive age; they also may be more careful when driving, or drivers may drive more carefully when an occupant of their vehicle is pregnant.

New Mexico is a sparsely populated, rural state where long distances must be traveled. The majority of the pregnancy-associated motor vehicle fatalities occurred on highways in rural areas.

In New Mexico, minority populations (Hispanic and American Indian males) are at higher risk of motor vehicle fatalities.[14] In our study, Hispanic and American Indian women were overrepresented among pregnancy-associated motor vehicle fatalities. Prenatal health care profes-

sionals serving minority populations need to be particularly vigilant about prenatal education regarding seat belt use.

In 1994, 52% of all fatal motor vehicle crashes in New Mexico involved alcohol[12] compared with 45% in our study. Alcohol-related crash fatalities can be reduced by strictly enforcing drunk driving laws, lowering the social acceptance of driving while intoxicated, and counseling pregnant women not to ride with intoxicated drivers.

The most important modifiable risk factor identified in this study is seat belt use:more than 75% of the pregnant and postpartum women who died were not wearing seat belts. The American College of Obstetricians and Gynecologists recommends that prenatal health care professionals counsel their patients on seat belt use throughout pregnancy.[15] In a recent study of motor vehicle crashes during pregnancy, Wolf et al. found that compared with restrained pregnant women, unrestrained pregnant women had increased risks for a low birth weight baby and for delivery within 48 hours after the crash.[16] In a previous survey, only 42% of pregnant women in New Mexico reported always using their seat belts.[17] Nearly a third were unsure of the safety of seat belt use during pregnancy, and one-quarter did not know the correct way to wear a seat belt when pregnant. (The seat belt should be worn with the lap belt beneath the pregnant woman's abdomen and the shoulder belt between her breasts.) The general population knows the correct way to wear a seat belt and that seat belt use reduces serious injury and death in the event of a crash, but pregnant women need advice specific to their condition. Prenatal health care professionals—particularly those serving minority populations—need to emphasize proper seat belt use.

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Conferences and Reviews

Hepatitis G Virus:
Is it a Hepatitis Virus?

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Hepatitis G virus (HGV) and GB virus C (GBV-C) are two newly discovered viral agents, different isolates of a positive-sense RNA virus that represents a new genus of *Flaviviridae*. The purpose of this review is to analyze new data that have recently been published on the epidemiology and associations between HGV and liver diseases such as posttransfusion hepatitis, acute and chronic non-A–E hepatitis, fulminant hepatitis, cryptogenic cirrhosis, and hepatocellular carcinoma. The role of HGV in coinfection with other hepatitis viruses, the response to antiviral therapy, and the impact of HGV on liver transplantation are also discussed. HGV is a transmissible blood-borne viral agent that frequently occurs as a coinfection with other hepatitis viruses due to common modes of transmission. The prevalence of HGV ranges from 0.9 to 10% among blood donors throughout the world and is found in 1.7% of volunteer blood donors in the United States. The majority of patients infected with HGV by blood transfusion do not develop chronic hepatitis, but hepatitis G viremia frequently persists without biochemical evidence of hepatitis. Serum HGV RNA has been found in 0 to 50% of patients with fulminant hepatitis of unknown etiology and 14 to 36% of patients with cryptogenic cirrhosis. The association between HGV and chronic non-A–E hepatitis remains unclear. Although HGV appears to be a hepatotrophic virus, its role in independently causing acute and chronic liver diseases remains uncertain.

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Viral hepatitis is a major problem worldwide and is caused by five well-characterized etiologic agents.* Hepatitis viruses A, B, C, D, and E are distinct viruses whose molecular structure and disease associations are well known. All five viruses can cause acute hepatitis, but only hepatitis B, C and D can result in chronic infection. With the advent of precise serological and virological testing for all five viruses, it was recognized that 5 to 15% of patients with acute or chronic viral hepatitis were negative for all viral markers and had an illness operationally termed non-A–E hepatitis. A novel agent called hepatitis F virus was described as a new, enterically transmitted virus,[1] but this observation has not been confirmed and was likely a premature designation. Another hepatitis virus, the hepatitis G virus (HGV),[2] which appears to be the same virus as GB virus C (GBV-C),[3] has been identified, confirmed, and cloned. Two recent reviews on HGV[4,5] offered limited information on the clinical relevance of HGV in various diseases. The most recent information on HGV available in the literature, primarily in abstract form, constitutes the basis of this review. Hepatitis G virus, or GBV-C, infection has also been reported to be associated with various diseases such as aplastic anemia;[6,7] however, this review will focus mainly on the association of HGV with various liver diseases such as posttransfusion hepatitis, fulminant hepatitis, acute and chronic non-A–E hepatitis, and cryptogenic cirrhosis.

*See also the Editorial by Herbert L. Bonkovsky, "The Alphabet Soup of Viral Hepatitis: Is G a New Flavi(or) in the Mix?," on pages 49–50 of this issue.

Historical Perspective

Following the discovery of hepatitis C virus (HCV) in 1989,[8] it was recognized that there was a residual small percentage of community-associated and posttransfusion hepatitis cases caused by an unidentified viral agent. In addition, it had long been speculated that there were more than one non-A, non-B (NANB) transfusion-associated viral agents on the basis of chimpanzee cross-challenge studies and the observation that there was a chloroform-sensitive and a chloroform-resistant infectious agent.[9] Recent investigation led to the independent discovery of HGV[2] and GBV-C,[3] which were found to be different isolates of the same virus with >95% amino acid homology.[10]

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ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control and Prevention
ELISA = enzyme linked immunosorbent assay
GBV-C = GB virus C
HBV = hepatitis B virus
HCV = hepatitis C virus
HGV = hepatitis G virus
NANB = non-A, non-B
NIH = National Institutes of Health
NS = nonstructural
ORF = open reading frame
PCR = polymerase chain reaction
RNA = ribonucleic acid
SGPT = serum glutamate pyruvate transaminase
UTR = untranslated region

A GB hepatitis agent isolated from serum obtained from a 34-year-old surgeon (whose initials are GB) during the third day of jaundice was serially passed in the experimental animal, *Sanguinus sp.* (tamarin). Using representational difference analysis to clone the nucleotide sequences from the serum of a tamarin infected with the GB hepatitis agent, investigators at Abbott Laboratories discovered two flavivirus-like genomes which were called GBV-A and GBV-B.[11,12] It was later determined that GBV-A and GBV-B were most likely nonhuman viruses that only infect tamarins.[13] Human sera from individuals considered to be "at risk for non-A–E hepatitis" were screened for antibodies that recognize GBV-A and/or GBV-B recombinant proteins. Immunoreactive sera were subjected to polymerase chain reaction (PCR) using degenerative oligonucleotides capable of amplifying a segment of the putative helicase gene from GBV-A, GBV-B, or HCV. A PCR product from a West African specimen revealed a novel virus-like nucleotide sequence that was named GBV-C, which is most likely derived from a human virus.[3]

Simultaneously, researchers at Genelabs, using an immunoscreening technique similar to the strategy that led to the discovery of HCV, discovered a flavivirus-like sequence from a patient with NANB hepatitis, provisionally called hepatitis G virus.[2] Molecular cloning was performed from the plasma of a US patient with NANB hepatitis obtained through the Centers for Disease Control and Prevention (CDC) Sentinel Counties Studies of Viral Hepatitis. The patient was initially thought to be HCV-negative by the first-generation immunoassay but was subsequently found by the second-generation assay and PCR to be positive for HCV. Therefore, the original sequence of HGV was isolated from a patient who was coinfected with HCV. The HGV was found to be very closely related to GBV-C and to belong to the family *Flaviviridae*. The newly discovered viruses will be referred to as either GBV-C or HGV based on the terminology used in original studies, but will generally be referred to as HGV in this review.

Hepatitis G Virus

The genome of HGV is a positive-sense RNA that has sequence and organizational similarity to other viruses within the *Flaviviridae* family.[2,14] The original HGV isolate contains a continuous open reading frame (ORF) preceded by a 5′ untranslated sequence of 458 nucleotides and followed by a 3′ untranslated region (UTR) of 315 nucleotides. The ORF encodes a polyprotein of 2873 amino acids with a number of characteristic motifs: a helicase motif, two chymotrypsin-like protease motifs and an RNA-dependent RNA polymerase

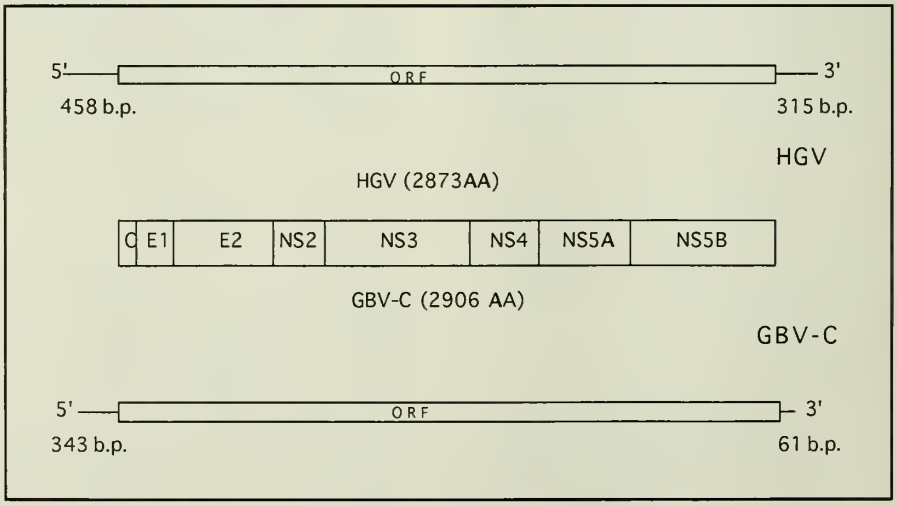

Figure 1. Genomic organization and comparison of the HGV and GBV-C. The viral genome has a single open reading frame (**ORF**) preceded by the 5′ untranslated region (**5′ UTR**) and followed by the **3′ UTR**. The open box represents the single ORF encoding the viral polyprotein, the thin line represents the 5′ UTR and 3′ UTR. Viral genome of HGV and GBV-C with sizes of the untranslated regions are shown in the upper and lower panel, respectively. The viral polyprotein encodes structural proteins, core (**C**) and envelope (**E1** and **E2**) followed by nonstructural regions (**NS2, NS3, NS4, NS5A,** and **NS5B**), and is shown in the middle panel with its size.

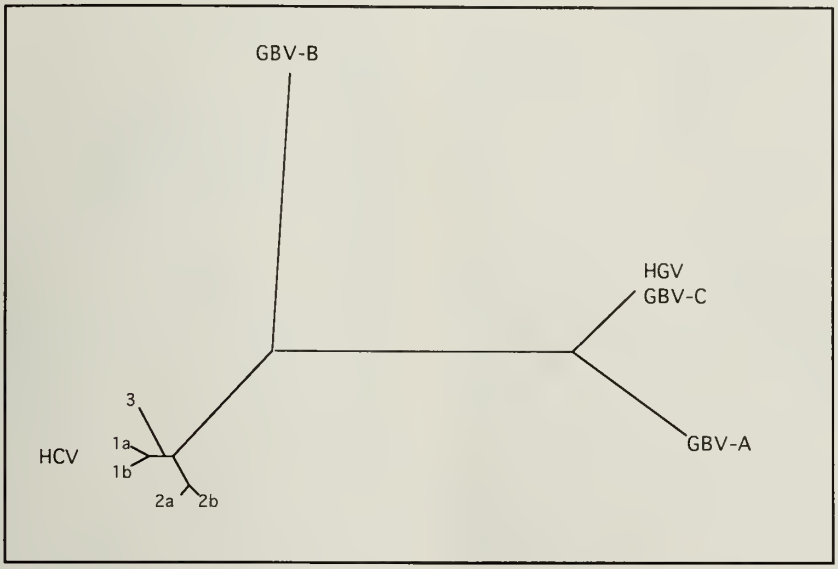

Figure 2. Unrooted phylogenetic analysis of the polyproteins of the GB agents (**GBV-A** and **GBV-B**), HGV, GBV-C, and various genotypes of hepatitis C virus (**HCV**). Modified from Leary et al.[14]

motif. The HGV genomic organization is similar to other members of the *Flaviviridae*, with the putative structural genes found at the 5′-end of the genome followed by putative nonstructural genes (Figure 1). The 5′ UTRs are highly conserved. The GBV-C is 9125 nucleotides in length, with a continuous ORF encoding a polyprotein of 2906 amino acids. This ORF is preceded by 343 nucleotides and followed by an additional 61 nucleotides of presumably untranslated sequence.[14] This polyprotein encodes an amino acid sequence motif consistent with a serine protease (in putative nonstructural 2 [NS2] region), a helicase (in putative NS3 region), and an RNA-dependent RNA polymerase (in the putative NS5B region). The GBV-C is more closely related to GBV-A (48% amino acid homology) than GBV-B (28% amino acid homology) or any of the HCV genotypes (29% amino acid homology with the HCV-1 isolate)[14] (Figure 2). The sequence similarity of HGV polyprotein is 43.8% identical to GBV-A, 28.4% identical to GBV-B, and 26.8% identical to HCV. The 331 nucleotides of the putative NS3 region of GBV-C show an 85.5% nucleotide identity and a 100% amino acid identity with the corresponding region of HGV. Alignment of the entire encoded polyprotein sequences of HGV with that of GBV-C shows 85% homology at the nucleic acid level and 95% at the amino acid level.[10] Therefore, these two viruses should be considered as different isolates of the same virus. Since this newly discovered virus is distinct from all other known flaviviruses including HCV, it is felt to form a new genus in the *Flaviviridae* family (Figure 2).

There is genetic heterogeneity among isolates from different geographic regions.[15–18] Phylogenetic analysis of the 5′ noncoding region of 146 HGV isolates from 16 different countries showed that there were three major subtypes: GBV-C and HGV as the prototype of two subtypes, and a new subtype commonly found in Asia.[15] Analysis of the 5′ noncoding region of HGV isolates from sera of Japanese patients showed that the degree of genetic differences between the Japanese isolates was similar to the subtype differences found in HCV; but when the Japanese isolates were compared with the prototypes, the degree of genetic differences corresponded to that found between different HCV genotypes.[16] The average similarity of the putative helicase region (NS3 region) of 21 Taiwanese GBV-C isolates to those from West Africa, East Africa, Canada, and the US were 83, 85, 78, and 82%, respectively.[17] All the Taiwanese isolates could be further classified into at least three groups. Therefore, there is genetic heterogeneity of HGV isolates from around the world, and HGV can probably be grouped into genetically distinct genotypes and subtypes as in the case of HCV. The significance of this genetic heterogeneity has yet to be determined but might explain the different rate of diseases associated with HGV in various studies.

Diagnosis of HGV Infection

Until the development of a serological assay from a highly-conserved region of HGV, infection can only be diagnosed by PCR assay to detect the viral RNA in serum. Since this assay detects only viral RNA, it will not be able to detect past infection as in the case of an antibody assay. In addition, conditions used for storage of serum are probably important since RNA is unstable. Sensitivity of the PCR assay will also depend on the choice of the PCR primers. The original primer set used by researchers from Genelabs were sequences derived from the putative NS5a region, and the PCR assay using these primers has a sensitivity of 200 copy equivalents

per milliliter of serum/plasma.[2] The primers that were developed by Simons et al.[3] were based on sequences from the putative NS3/helicase region. Using consensus oligonucleotide primers from the most highly conversed regions derived from eight GBV-C isolates, Leary et al.[19] were able to detect GBV-C RNA from 10 of 76 (13.2%) patients with non-A–E hepatitis compared with only four (5.3%) patients using a primer set and methods originally described by Simon et al.[3] This study clearly demonstrates the importance of primer selection and PCR protocols. A commercial PCR kit for detection of HGV RNA is available in Europe but not in this country (Hepatitis G virus probe set, Boehringer Mannheim GmbH, cat no. 1 782 720).

An enzyme-linked immunosorbent assay (ELISA) for detection of antibodies to recombinant HGV putative envelope protein E2 was recently described as a potential serological marker for immunity to HGV infection.[20] Antibodies to E2 were found in 9% of 80 healthy German blood donors, all of whom were HGV RNA negative. Antibodies to E2 were found in 41 of 99 intravenous drug users in Germany, but only four were viremic. Another 34 HGV RNA positive intravenous drug users were antibody negative. Among 11 Japanese patients with acute posttransfusion hepatitis (seven with HCV, three with hepatitis B virus [HBV] and one with non-A–E hepatitis) who were HGV RNA positive, all were initially antibody negative. Two of the four patients that subsequently developed antibodies to E2 became HGV RNA negative. These data suggest that antibodies to E2 might be a serological marker for diagnosing recovery from HGV infection, but further studies are necessary. Detection of HGV RNA by PCR remains the only established test for diagnosis of HGV infection.

Table 1.—*Prevalence of Serum HGV/GBV-C RNA Among Blood Donors*

Country	*%*
Japan	0.9
Spain	1.4–4.6
UK	3.2
Taiwan	4.2
Brazil	10
Australia	
Normal SGPT	4
Raised SGPT	5
US	
Accepted donations	1.7
Rejected donations (SGPT >45 IU/ml)	1.5

Epidemiology

Blood Donors

The prevalence of hepatitis G viremia among blood donors ranges from 0.9 to 10% (Table 1). Smaller series tend to report higher prevalence rates, which might reflect patient selection bias. Serum HGV RNA was detected in 1.7% of 779 consecutive U.S. volunteer blood donors with normal serum glutamate pyruvate transaminase (SGPT) levels. In contrast, HGV RNA was found in 11 (1.5%) of 709 donors who were rejected due to SGPT elevation.[2] In Queensland, Australia, HGV RNA was found in four of 100 blood donors (4%) with normal SGPT levels and in one of 20 (5%) with raised SGPT levels.[21] All 120 tested negative for antibodies to HCV, HIV-1, HIV-2, HTLV, and hepatitis B surface antigen and did not fall into any "at risk" group. One of the five HGV RNA positive patients was found to be HGV RNA negative on a prior plasma sample. His SGPT remained normal, and he had no identifiable risk factors for HGV infection. HGV has been detected in blood donors from other parts of the world with prevalence rates of 0.9% (4/448) in Japan,[22] 1.4% (14/1000)[23] and 4.6% (6/129)[24] in Spain, 2% (4/200) in Taiwan,[25] 3.2% in Edinburgh, UK,[26] 4.2% (21/500) in France,[27] and 10% (12/120) in Brazil[28] (Table 1). (The high 10% prevalence rate in Brazil, however, was based on the screening of only 120 blood donors.)

Using recombinant proteins from the putative core and NS genes NS3, NS4, and NS5 regions of GBV-B and nonstructural gene of GBV-A, researchers at Abbott Laboratories found the seroprevalence rate among US volunteer blood donors to be 1.2% (12/960) and 0.3% (3/860), respectively.[3] None was reactive for both viruses. Since GBV-A and GBV-B are nonhuman pathogens, these findings most likely represent cross-reactivity with proteins encoded by another related virus such as GBV-C. Serum GBV-C RNA was detected in only seven of 42 GBV-A and/or GBV-B seropositive West African samples. GBV-A or GBV-B RNA was not detected by PCR in any of the sera of 30 blood donors, 40 hemophiliacs, 30 intravenous drug users, 40 patients with chronic HBV/HCV infection, or 18 patients with acute or chronic non-A–E hepatitis.[29] Many of these patients were coinfected with HGV.

Transmission

HGV is a bloodborne virus that is parenterally transmitted. The strongest evidence that HGV is parenterally transmitted comes from prospective studies of posttransfusion hepatitis, in which other viral agents are excluded. HGV can be detected in sera of patients who were previously HGV negative after transfusion of blood from HGV positive donors. Sequence analysis of the NS3 region of HGV from two implicated donor and recipient pairs have shows striking sequence similarity (98 and 100%).[30]

The prevalence of HGV in populations exposed to multiple blood products and in intravenous drug users

has also been shown to be high. HGV was found in 5.4–18.6% of hemophiliacs[2,31,32] and 18% of anemic patients requiring multiple transfusions.[2] The majority of hemophiliacs who were HGV RNA positive were also coinfected with HCV (up to 75%).[33] The prevalence of HGV infection among patients on hemodialysis ranged from 3.1% in Japan[22] to 26% in Spain.[24] Serum HGV RNA was found in 12.5% of 120 hemodialysis patients in the US,[34] similar to the percentage in France.[35] Most patients who were infected with HGV/GBV-C alone had normal SGPT levels.[22,35] Serum HGV RNA was detected in 17 of 63 (27%) HCV RNA positive hemodialysis patients (Umlauft et al., unpublished observation). One study[22] found that 12 of 16 GBV-C RNA positive patients on maintenance hemodialysis had a history of transfusion, and GBV-C RNA was first detected 3 to 20 weeks after blood transfusion. Infection with GBV-C tended to persist in hemodialysis patients, and GBV-C disappeared from only one of eight patients followed for 7 to 16 years.

Among intravenous drug users, serum HGV RNA was found at rates of 33% in Europe,[2] 35% in Switzerland,[36] and 43% in Japan.[37] A study from the Los Angeles area found HGV RNA in only 12 of 124 (9.6%) intravenous drug users, and 11 of the 12 were coinfected with HCV.[34] In another study, up to 97% of the serum HGV RNA positive intravenous drug users were coinfected with HCV.[36]

Vertical transmission has also been reported. Three of nine babies born to HGV positive mothers became HGV RNA positive as assessed by PCR. One of the three was coinfected with HCV and the other two were coinfected with HIV.[38] In another case report from a HGV positive mother, the cord blood was negative and sera from the newborn at 4 and 6 weeks of age were HGV positive, suggesting that the infection occurred perinatally.[39]

There is currently no information on other modes of transmission. However, as in the case of HCV, many HGV positive patients have no identifiable parenteral risk factor.

Table 2.—*Prevalence of Serum HGV/GBV-C RNA in Patients With Various Liver Disease*

Liver Disease	*%*
Posttransfusion non-A–E hepatitis	12.5–15
Community-acquired acute non-A–E hepatitis	0–35
Fulminant hepatitis	0–50
Cryptogenic cirrhosis	14–36
Hepatocellular carcinoma	
HGV alone	8
HGV/HBV or HCV/HBV coinfection	4–12
Coinfection	
HGV/HBV	10–17
HGV/HCV	11–19

Associations of HGV with Liver Diseases

The association of HGV with liver diseases is based on prevalence of serum HGV/GBV-C RNA in such patients in some studies. The range of prevalence of HGV viremia in patients with various liver diseases is summarized in Table 2.

Posttransfusion Hepatitis (PTH)

Hepatitis C virus has been found to be the major viral pathogen that accounts for posttransfusion NANB hepatitis. The incidence of transfusion-associated hepatitis has markedly decreased with the screening of all potential donors for antibody to HCV (anti-HCV). There is always a group of patients in posttransfusion hepatitis studies whose illness cannot be attributed to hepatitis A, B, or C. In the National Institutes of Health (NIH) prospective PTH study, for example, 12% were non-A, non-B, non-C, suggesting that there was another transmittable viral agent.[40] The pursuit of such an infectious agent led to the discovery of HGV. HGV was isolated from the serum of one such patient although the patient was subsequently found to be coinfected with HCV (see discussion above).[2]

Although HGV is clearly a parenterally transmitted virus, its role as a cause of PTH is uncertain. There is a poor correlation between the presence of virus and chronic liver disease. Patients who develop chronic PTH are invariably coinfected with HCV, and chronic hepatitis correlates closely with HCV infection. In a large prospective study of PTH in Canada, the prevalence of HGV positivity by PCR in non-A–C PTH was 15% (3/20), or three in 4,588 blood recipients.[41] None of the three patients progressed to chronic liver disease, but HGV RNA persisted in one of the patients 5 years after recovery from PTH. Another prospective study of PTH showed that 40 of 400 patients who underwent cardiac surgery were GBV-C positive[25]: six were HGV positive before surgery, with five remaining viremic. Out of the 34 patients who became GBV-C positive after surgery, seven were coinfected with HCV and two were coinfected with HCV and HTLV-1. These 34 patients received blood products from a significantly higher number of donors than those not infected with GBV-C. The 25 recipients who became infected with GBV-C alone had a low mean peak serum SGPT of 31 IU/l. In this group, three had mild SGPT elevation (less than twofold the upper limit of normal), and two had peak SGPT levels of 101 and 123 IU/l, respectively, during the 6-month follow-up. All the patients who were infected with GBV-C alone were asymptomatic without evidence of hepatitis in the follow-up period of 1 to 8 years despite the persistence of GBV-C of up to 8 years. Serum GBV-C RNA occurred as early as 1 week after transfusion. The laboratory data and clinical course in the seven HCV coinfected recipients were similar to those infected with HCV alone. GBV-C was detected in only one of eight (12.5%) patients with non-A–E PTH. The risk of GBV-C transmission was esti-

mated to be approximately 0.46% per donor but rarely caused posttransfusion hepatitis. In fact, among all the cases of PTH that were felt to be associated with HGV viremia, the majority of studies[25,41–43] did not reveal progression to chronic hepatitis.

A prospective study of transfusion-associated hepatitis from the NIH showed that HGV RNA was found in nine of 79 patients with transfusion-associated NANB hepatitis, with six patients coinfected with HCV.[44] The disease in the three patients with HGV RNA as the only identifiable viral marker was mild, and only one remained persistently viremic with elevated SGPT levels for 4 years before dying from unrelated causes. The hepatic injury in the HCV/HGV coinfected patients was not different from the disease in those infected with HCV alone. An additional 12 patients with minor SGPT elevations that did not meet the study criteria and in 14 patients with no hepatitis were also HGV RNA positive. There was no significant difference in the proportion with HGV infection among the transfusion recipients with or without hepatitis. Therefore, most acute HGV infection associated with transfusion occurred without evidence of hepatitis. HGV infection, however, was found to be associated when compared with controls.

Therefore, even though it is well-documented that HGV is transmitted through blood, it is rarely a cause of PTH. There has been a decline in the incidence of PTH with the introduction of second-generation assays for screening of HCV, and in several recent studies, the incidence of posttransfusion SGPT elevation was no different from the nontransfused control population.[45,46] This suggests that some of these PTH cases represent "background hepatitis" or nonviral etiologies related to perioperative events.

Acute Community-Acquired Non-A-E Hepatitis

The evidence that there might be another viral agent accounting for community-acquired non-A–E hepatitis is stronger than in the case of PTH. Data from the CDC showed that only 82% of the NANB community-acquired acute hepatitis in the sentinel counties was caused by HCV.[47] A study from Greece showed that 47% of community-acquired NANB hepatitis is anti-HCV negative.[48] In Spain, 19% of acute hepatitis was classified as non-A–E.[49] Since hepatitis D always exists as a coinfection with HBV and hepatitis E virus is rarely a cause of acute hepatitis except in certain geographic areas such as India, all these non-A, non-B, non-C hepatitis cases are considered to be non-A–E hepatitis. A recent study found a very high prevalence of GBV-C in a group of Italian patients with hepatitis of unknown etiology.[50] Serum GBV-C RNA was found in 11 of 31 (35%) patients with acute non-A–E hepatitis and in seven of 18 (39%) with chronic hepatitis. Among 18 patients who were GBV-C positive, only one had a history of transfusion and three had used intravenous drugs. The lack of serum samples prior to the onset of disease preclude a definitive link between GBV-C infection and the onset of hepatitis.

Of the 38 patients identified as having community-acquired non-A–E hepatitis in four U.S. sentinel counties from 1985 to 1993, five (13%) were HGV RNA positive at the time of their acute illness. Four of the five remained HGV RNA positive over a follow-up period of 2–9 years, and none developed chronic hepatitis.[2] A follow-up study[51] showed HGV RNA in 25% of 100 patients with hepatitis A, 32% of 100 patients with hepatitis B, 20% of 116 patients with hepatitis C, but only 9% of 45 patients with non-A–E acute community-acquired hepatitis. The four patients with HGV alone had a median SGPT of 1680 IU/l (range, 200–3240 IU/l), a median bilirubin of 9.6 mg/dl (range, 0.6–30.9 mg/dl), and a median age of 27. The clinical characteristics of the acute illness were similar for patients with HGV alone and those with hepatitis A, B, or C with or without HGV infection. and HGV coinfection did not affect the clinical course. Chronic hepatitis developed in 60% of patients with HCV infection alone, compared with 61% of the HCV-HGV coinfected group. None of the HGV group alone developed chronic hepatitis even though three (75%) were persistently HGV positive for a follow-up period of 1 to 9 years. Based on the findings of this study, it was estimated that 0.3% of acute viral hepatitis may be infected with HGV alone.Therefore, HGV is not a major cause of acute community-acquired hepatitis in the US. Similarly, none of the 29 Japanese patients with acute non-A–C hepatitis was HGV RNA positive.[52]

HGV Coinfection with Other Hepatitis Viruses

Most of HGV infection occurs in the setting of coinfection with other hepatitis viruses such as HBV and HCV. This coinfection is probably related to similar modes of transmission. However, HGV appears to have little impact on the course of infection, and the clinical course is largely determined by the coinfecting virus. In Europe, HGV was found to coinfect seven of 72 (10%) patients with chronic HBV, and 18 of 96 (19%) patients with chronic HCV.[2] HGV coinfection was found in 11% of 99 US patients with chronic HCV infection, and the coinfection was not associated with detectable differences in viral load, HCV genotype, demographic features, or histological severity of liver disease.[53] The clinical course of seven posttransfusion GBV-C and HCV coinfected patients was similar to those infected by HCV alone.[25] Tanaka et al.[54] found that 21 of 189 (11%) Japanese patients with chronic hepatitis C were coinfected with HGV and found no difference between this group and those who had HCV infection alone in terms of clinical presentation (liver enzyme elevation, liver histology, history of transfusion), HCV RNA levels, or response to interferon therapy. The coinfected patients were generally younger.[54,55] Serum HGV RNA levels also decreased during interferon therapy, but only two of nine patients studied had a sustained response. The effects of interferon on GBV-C and HCV were independent.[54,55,81]

Marrone et al.[56] found HGV RNA in 18 (17%) of 104 patients with chronic hepatitis B, but found little effect of HGV infection on the course of hepatitis B or

response to interferon therapy. During interferon therapy, HGV RNA became undetectable in all 13 serially tested patients, but levels returned to pretreatment values after interferon was stopped.

In summary, serum HGV RNA is found in approximately 10–20% of patients with chronic hepatitis B or C infection but has little or no impact on the clinical course or response to interferon therapy.

Fulminant Hepatitis

Thirty to fifty percent of fulminant hepatitis cases from the US are NANB hepatitis,[57,58] suggesting the presence of another infectious agent that causes fulminant hepatitis. HCV was found to be an unusual cause of fulminant NANB hepatitis, and some cases actually represented serology-negative HBV infection.[59] A togavirus-like particle has also been found in some patients with NANB fulminant hepatitis.[60]

Yoshiba et al.[61] found GBV-C RNA in the serum of three of six Japanese patients with fulminant hepatitis of unknown etiology. All six patients were seronegative for all known hepatitis viruses, and five of the six eventually died of hepatic failure. All six patients were also subsequently shown to be HBV and HCV negative by PCR.[18] Of the three patients who were GBV-C positive, one had a history of transfusion, one was a nurse, and one had a history of acute self-limited NANB hepatitis. Kuroki et al.,[62] however, were unable to detect GBV-C from seven Japanese patients with fulminant hepatitis without any history of transfusion or acute hepatitis. All seven patients were seronegative for hepatitis A–D and were PCR negative for HBV, HCV, and HEV. One of the seven patients was GBV-C negative on admission, but one sample taken after transfusion was positive. As with the other series, all seven patients except the last case (who became GBV-C positive) died from hepatic failure. Several larger series from Japan found GBV-C/HGV to be uncommon among Japanese patients with fulminant hepatitis of unknown etiology. Serum HGV/GBV-C RNA was not detected in series of 26[63] and 10[64] Japanese patients with fulminant hepatitis. The study by Ishikawa et al.[52] found HGV RNA in only one of 21 patients with fulminant hepatitis, and this patient was also one of the four patients with fulminant hepatitis who were HCV RNA positive.

Data from the National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplant Database showed that nine of 39 (23%) US patients with fulminant hepatic failure were HGV RNA positive before transplant.[65] There was no significant difference in the clinical and biochemical features between the HGV positive and negative groups. Most HGV RNA positive patients pretransplant remained positive at follow-up. However, most of the HGV PCR positive patients posttransplant acquired the infection de novo. Munoz et al.[66] found HGV RNA in 13 (36%) of 36 US patients with non-A–C fulminant hepatitis.

Among 131 patients admitted to a liver transplant unit in Scotland for fulminant hepatitis from 1992 to 1995, only five of 23 consecutive patients with non-A–E fulminant hepatitis were GBV-C RNA positive.[26] All five were GBV-C RNA positive using primers from the highly conserved 5′ noncoding region, but only four of the five were positive with primers from the NS3 region. All five patients were young (mean age 21) with relatively short duration of disease (mean of 25 days) and mean SGPT peak of 729 IU/l (range, 335–1494 IU/l). All five patients had received blood products during their hospitalization prior to testing positive for GBV-C RNA. Only two patients had sera available after the onset of hepatitis but prior to transfusion and both were negative for GBV-C RNA. This suggested that patients might be infected through transfusion after the onset of hepatitis. Two of the five patients died and two underwent liver transplantation. One patient who underwent liver transplantation was GBV-C RNA negative in a 5-month follow-up sample. One of the two patients who were initially GBV-C RNA negative recovered from fulminant hepatitis and was GBV-C RNA negative when retested 1 year later. This study suggests that GBV-C is unlikely to be a cause of fulminant hepatitis.

Studies from Germany found GBV-C RNA in one of 12 (8%)[67] and 12 of 24 (50%)[68] patients with fulminant hepatic failure. HGV RNA was detected in six of 21 (28%) Spanish patients with idiopathic fulminant hepatitis.[69] It is not clear if the wide differences in the incidence of HGV infection in patients with fulminant hepatitis from various series (0 to 50%) is related to differences in the genomic heterogeneity of HGV[15–18] or

Table 3.—*Prevalence of Serum HGV/GBV-C RNA in Liver Transplant Recipients*

Underlying Liver Disease	No. of Patients	HGV/GBV-C RNA Positive: Pretransplant %	HGV/GBV-C RNA Positive: Posttransplant %
Cryptogenic cirrhosis	14	36	71
Cryptogenic cirrhosis	45	20	67
Cryptogenic cirrhosis	70	16	54*
Fulminant hepatitis	39	23	

*54% of 69 patients who were HGV RNA negative before liver transplant for cryptogenic cirrhosis or fulminant hepatitis became HGV RNA positive posttransplant.

sensitivity of the PCR assays.[19] Most of these studies are retrospective, and the PCRs were performed on stored serum, which might have effects on the reliability of HGV RNA by PCR.

Cryptogenic Cirrhosis

Some patients who have chronic hepatitis and cirrhosis of unknown etiology may undergo liver transplantation. The reported prevalence of HGV in general appears to be related to the severity of liver disease. None of 26 Japanese patients with non-B, non-C chronic hepatitis was HGV RNA positive.[70] GBV-C RNA was found in two (6%) of 32 patients with cryptogenic chronic liver disease without cirrhosis[71] but in two of 14 (14%) patients with cryptogenic cirrhosis.[72] Among patients with advanced cryptogenic cirrhosis requiring liver transplantation, the prevalence of HGV before liver transplantation was 11 of 70 (16%)[65] and four of 19 (22%)[73] in the US and five of 14 (36%) in Italy.[74] The prevalence was much higher after liver transplantation (see discussion below).

HGV Infection in Liver Transplantation

Most patients who are serum HGV RNA positive before liver transplantation remain positive after transplant (Table 3). However, most HGV infections posttransplant are acquired de novo and are most likely related to the use of blood products at the time of surgery. In an Italian study, HGV RNA was found in five of 14 (36%) patients with cryptogenic cirrhosis before liver transplant, but was detected in 10 patients (71%) after transplant.[74] All patients who were HGV positive before liver transplantation had persistent infection posttransplant. Similarly, the prevalence of HGV RNA was found to be 20% in patients with cryptogenic cirrhosis before liver transplant but increased to 67% posttransplant.[75] In a group of 69 patients with either cryptogenic cirrhosis or fulminant hepatitis who were HGV negative before liver transplant, 38 or 69% became positive after transplant.[65] However, there appeared to be no association between HGV infection and patient survival,[76] graft survival,[65] or posttransplant hepatitis.[76] As with HCV, the mean HGV RNA level as determined by bDNA assay was significantly higher at 1 year posttransplant than the mean pretransplant titers.[73] Therefore, HGV infection was very common with liver transplantation, and viremia usually persisted after liver transplantation in patients who were HGV RNA positive before liver transplantation. However, HGV infection by itself has little or no impact on the graft or posttransplant course.

Hepatocellular Carcinoma

Serum HGV RNA has been found in patients with hepatocellular carcinoma (HCC). HGV RNA was found in only one of 28 HCV-infected patients with HCC.[77] Among patients transplanted with HCC, HGV RNA was found in four of 34 patients of whom three were coinfected with HCV and one was coinfected with HBV.[78] GBV-C RNA was found in 11 of 111 (10%) cases of HCC in Japan, but 10 of 11 were coinfected with HCV and one with HBV. HGV RNA was found as the only infectious viral agent in seven (8%) of 85 Austrian patients with HCC.[79] Since the majority of patients with HCC were coinfected with either HBV or HCV, the role of HGV in the etiology of HCC is unclear. Therefore, with the exception of the Austrian study,[79] HGV is unlikely to be a major etiologic agent of HCC.

Response of HGV to Antiviral Therapy

There are no data on treatment of patients who are infected with HGV alone, since the role of HGV as a cause of chronic viral hepatitis has yet to be determined. Studies of patients coinfected with HCV who were treated with interferon showed that HGV is sensitive to interferon therapy. The responsiveness of HCV and HGV appeared to be unrelated, and biochemical response to interferon therapy was correlated with HCV alone.[53–55,81] As in the case of HCV, most of the decrease or disappearance of HGV RNA during interferon therapy was transient, and reappearance of HGV RNA was very common. Tanaka et al.[54] found that only two of the nine HGV/HCV coinfected patients studied had a sustained HGV response to interferon therapy. Neither patient cleared HCV RNA. Three of the patients who had sustained response to HCV did not clear HGV RNA, but SGPT levels remained normal despite reappearance of HGV RNA after interferon therapy. Another study showed that HGV RNA level decreased and even become undetectable during therapy among two patients coinfected with HBV and six patients with HCV treated with interferon. However, HGV RNA returned to pretreatment levels in all patients after interferon was stopped, including the HCV coinfected patient with sustained response with normal SGPT.[29] We found similar results in a group of HGV/HCV coinfected patients on hemodialysis who were treated with interferon. All 10 coinfected patients were HGV RNA negative at the end of interferon therapy but only three remained so after 1-year follow-up, and the response was independent of that of HCV (unpublished observation). In contrast to interferon, ribivarin has little effect on serum HGV RNA levels.[80,81]

Summary

This paper reviews current information on the newly discovered viral agent, HGV. The information summarized in this review came from two sources: a Medline search of all papers published in the literature and review of abstracts from recent scientific meetings. Since this is a rapidly changing field, the most recent information is published as abstracts and as such should be considered preliminary in nature. Moreover, some of the series contained only small number of patients or were published as a letter to editors. The findings of larger series should be considered more significant than smaller series.

The association between HGV and chronic hepatitis

is unclear. The prevalence of hepatitis G viremia was the same among blood donors with normal and elevated SGPT levels in both US and Australia studies.[2,21] The detection of HGV RNA in patients with various types of liver disease does not necessarily mean that HGV is the cause. Interpretation of current data is hampered by several factors. First, HGV can only be diagnosed using a PCR technique. Some of the differences in the prevalence of HGV among various groups might be the result of differences in PCR techniques or storage conditions of serum. PCR assay using primers from a highly conserved region such as sequences from the 5′ UTR is likely to be more sensitive than assays using primers from a less conserved region such as NS3.[26] Differences in primer sets and running condition can result in more than twofold differences in sensitivity (13.2 vs 5.3%).[19] Second, it is possible some of the observed differences of prevalence of HGV/GBV-C reported in the literature are the result of differences in the virulence of different isolates. Even though the prototype HGV and GBV-C are found to be different isolates of the same virus, there are differences in length and at the amino acid level. Heterogeneity in GBV-C genomic sequences has been reported.[15–18] Third, HGV commonly occurs as a coinfection with another hepatitis virus, usually HCV. This might be related to the common mode of transmission, such as transfusion. However, most existing data suggest that HGV coinfection does not alter the clinical course of chronic hepatitis B or C in these patients.

In studies that investigate the "natural history" of chronic HGV infection, such as prospective studies on transfusion associated hepatitis, there is a poor correlation between serum HGV RNA and the level of SGPT elevation.[44] The majority of patients do not develop chronic hepatitis.[25,41–43] Similarly, there is no relationship between HGV virological response and biochemical response to interferon therapy in patients coinfected with HGV/HCV.[53–55,81] These findings show that hepatitis G viremia frequently occurs in the setting without SGPT elevation, that is, biochemical evidence of hepatitis. Therefore, it is not clear that HGV is indeed a cause of chronic hepatitis. The finding of HGV/GBV-C RNA in serum of patients with fulminant hepatitis of unknown etiology (0[62–64] to 50%[61]) and cryptogenic cirrhosis (14[72] to 36%[74]) could be fortuitous. One of the most interesting findings of several groups is the unexplained high prevalence of HGV infection after liver transplantation, even though the HGV infection did not alter the clinical course in these patient or affect graft survival. Since the role of HGV as a etiologic agent of liver disease is unclear, therapy is not recommended at this point. Interferon could be used if HGV were to be demonstrated as a cause of liver disease. The development of a reliable serological assay should resolve some of these unanswered questions.

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Epitomes

Important Advances in Clinical Medicine

Pathology

Yutaka Kikkawa, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in pathology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Pathology of the California Medical Association, and the summaries were prepared under the direction of Yutaka Kikkawa, MD, and the panel.

Laboratory Work-Up of Patients With Heritable Thrombotic Disorders

THE EVALUATION OF PATIENTS with heritable thrombotic disorders has been improved by several diagnostic breakthroughs. In 1993, after it was observed that plasma samples from some individuals with inherited thrombophilia were resistant to the anticoagulant action of activated protein C, it was discovered that this resistance was due to a point mutation in the heavy chain of the factor V molecule (arginine 506→glutamine) toward which activated protein C is targeted. This mutation has an incidence of about 5% in individuals of European Caucasian ancestry and is the most common cause of hereditary thrombophilia. It accounts for about 21% of all cases of thrombosis. In heterozygotes and homozygotes, the risk of thrombosis is increased 5- to 10-fold and 50- to 100-fold, respectively, over that of the general population.

Although the defect can be screened for by a modified activated partial thromboplastin time (APTT) test mixing patient plasma with and without activated protein C ("activated protein C resistance testing"), confirmation of the presence of the gene defect (referred to as "factor V Leiden") requires DNA analysis. With an incidence of 5% in the general population, it is not surprising that this defect is characterized as one with low penetrance, since it affects only a small percentage of those individuals that do carry it. In fact, clinical expression may often require the presence of another risk factor, either hereditary or acquired. Because of the low penetrance, mass screening programs for this abnormality are not advocated.

In 1994, a relationship between mild hyperhomocysteinemia and venous thrombosis was clearly demonstrated, although the association between homocysteinemia and arterial thrombosis had been known as far back as the 1960s. Mildly increased levels of homocysteine, a sulfhydryl amino acid enzymatically derived from methionine, were found to occur in about 20% of patients with juvenile venous thrombosis. In addition, increased levels of homocysteine have been found in 10% of patients with first-time thrombosis.

In the general population, enzyme defects that can cause hyperhomocysteinemia have a frequency of about 0.5%. More commonly, the disorder is acquired secondary to nutritional deficiencies of folate, B_{12}, and pyridoxine—especially in older adults—even with normal serum vitamin levels. Hyperhomocysteinemia can be diagnosed by measuring fasting plasma levels, since those reference ranges are most readily available, although some have advocated measuring plasma levels after oral methionine loading as a more sensitive assay. If diagnosed, whether acquired or hereditary, daily doses of vitamins have been recommended in adults: 1 mg folic acid, 0.4 mg cobalamin, and 100 mg pyridoxine (the latter of which is 50 times the recommended daily allowance).

In comparison to the 21% incidence of factor V Leiden in unselected patients with thrombosis, other less common causes of hereditary thrombophilia include protein C deficiency, protein S deficiency, and antithrombin III deficiency, with incidences of 3, 2, and 1%, respectively, in the general population. Deficiencies of protein C and antithrombin III are best diagnosed by using functional assays rather than immunoassays. Deficiencies of protein S are best determined using immunoassays, since functional assays for protein S can be falsely positive due to the presence of activated protein C resistance.

Two important nongenetic causes of thrombophilia to be considered in an initial laboratory screen for risk factors are the lupus anticoagulant and hyperlipidemia. Some uncommon genetic risk factors for thrombosis include dysfibrinogenemia, plasminogen deficiency, tissue plasminogen activator deficiency, excess plasminogen activator inhibitor, and heparin cofactor II deficiency.

If an asymptomatic individual with hereditary thrombophilia (excepting hyperhomocysteinemia) is exposed to an additional risk factor for thrombosis, including immobilization in bed, pregnancy, and major surgery, prophylactic treatment with subcutaneous heparin may be indicated. If an individual with hereditary thrombophilia has a life-threatening thrombotic episode, another genetic defect, or a sustained lifelong risk factor, long-term prophylactic anticoagulant therapy with coumadin may be indicated.

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Determining the Number of Copies of HIV-1 RNA in Plasma: Applying This New Test to Management of Patients

THE ABILITY TO DETERMINE the number of copies of HIV-I RNA in plasma, also known as "viral load," has added a valuable tool to the clinical armamentarium available for the management of patients with HIV-1 infection. Several laboratory procedures are now at hand to perform these quantitative studies, including reverse-transcriptase polymerase chain reaction (RT-PCR), branched DNA (bDNA), and nucleic acid sequence-based amplification (NASBA). All of these methods have been found to be highly reproducible, and the results obtained with the three systems have shown good correlation.

In patients who are infected with HIV-I, the number of HIV-I RNA copies rapidly increases over a period of several weeks until the immune system mounts a response to the virus. As a result of the immune response, the number of HIV-I RNA copies decreases and remains stable for several years. During the late stages of infection, after a decline of the immune defenses, the replication of the virus cannot be controlled and the number of copies increases again. Thus, in general, there is an inverse correlation between the number of $CD4^+$ cells, indicative of the immune response, and the number of HIV-1 RNA copies in plasma.

Based on several in vitro and in vivo studies, it is estimated that the life cycle of HIV-1 is 2.6 days, from the time that it infects a cell until the new progeny are produced, with a half-life in plasma of 6 hours. About 10 billion virions are produced per day in an infected individual. In clinically stable patients, the plasma HIV-1 RNA levels are fairly stable until the patient's health deteriorates or antiviral therapy is modified.

There are now several situations in which determining the number of copies of HIV-1 RNA in plasma is clinically useful. One is as a prognostic tool shortly after infection. Individuals in whom the number of RNA copies is >100,000/ml within 6 months from seroconversion are 10 times more likely to progress to AIDS over a 5-year period than those with <100,000 copies/ml. Furthermore, fewer than 30% of patients with <10,000 copies/ml died within 10 years, while over 70% of those with an RNA count >10,000 progressed to AIDS and died in a 10-year period.

Determining the plasma HIV-I RNA levels is also useful in evaluating the efficacy of antiretroviral therapy. In general, it is recommended that basal HIV-1 RNA levels be determined twice over a 2- to 4-week interval before initiating therapy. Although the number of RNA copies per milliliter should decrease below 5,000 following therapy, a decrease of at least 0.5 log in the number of viral copies is considered to indicate effective activity. These measurements should be made 3 to 4 weeks after starting or changing therapy. They should be repeated every 3 to 4 months, along with the $CD4^+$ counts, in order to determine the effectiveness of the antivirals in maintaining a low viral load. A return to pretreatment values indicates that the drugs have failed to control the progression of the viral infection.

The HIV-I viral load test has also been used as a predictor of perinatal transmission. The higher the number of HIV-1 RNA copies detected in the mother's serum late in gestation or at the time of delivery, the higher the risk of transmission of the virus to the newborn. For example, in one study, no women with <20,000 HIV-I RNA copies/ml transmitted the virus to their newborns, while all mothers with >80,000 copies/ml did. Also, the viral load test helped to follow up on antiretroviral therapy and determine its effect on the transmission of the virus from the mother to the offspring.

In conclusion, measurement of the number of HIV-1 RNA copies in plasma, in conjunction with other clinical and laboratory parameters, can help evaluate the prognosis, staging, and progression of HIV-I infection and assess the efficacy of antiretroviral therapy.

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Laboratory Detection of *Chlamydia trachomatis*

Chlamydia trachomatis infection is the leading cause of sexually transmitted diseases in the Western world. Lower genital tract infections in females are frequently asymptomatic and therefore undetected. Infections by *C trachomatis* can involve the upper genital tract as well, leading to tubal scarring and infertility. Neonatal infections due to exposure at birth are also well-established complications. For these reasons, routine screening is recommended for those most at risk of developing a *C trachomatis* infection—sexually active adolescents and women in their early twenties and those with new sexual partners.

Tests for the laboratory detection of *C trachomatis* are based on detecting antigen, nucleic acid, or viable organisms. Since there are major differences in the performance, sensitivity, and specificity of these tests, it is important to understand these distinctions.

The first laboratory test available, the culture, was until recently the gold standard of *Chlamydia* testing. Its specificity of 100% makes it the only recommended test for children or victims of sexual abuse. Culture should detect even a single viable *Chlamydia* organism, but its sensitivity can be compromised by variables such as loss of viability upon transport or storage, differences in susceptibilities of cell lines, and stains used in the culture technique. Furthermore, there is no standard culture method, so results vary widely between laboratories.

The first commercially available assays were based on the detection of chlamydial antigens using polyclonal and/or monoclonal antibodies that recognize either the major outer membrane protein or lipopolysaccharide of the organism. Today, antigen detection tests range from a 20-minute paper- or wafer-based assay to a 3- to 4-hour enzyme immunoassay (EIA). The specificity of the assays is, with few exceptions, acceptable (>98%). Reported sensitivities of these tests vary tremendously, neutralizing any comparison based on literature review. Most evaluations of the antigen-based assays have used culture as a gold standard but, since the sensitivity of the culture method can vary, the apparent sensitivity of the antigen detection method fluctuates. When DNA amplification methods are run in parallel with culture, the sensitivity of the antigen-based assays ranges between 50 and 70%. Therefore, while these assays may be convenient in terms of time, simplicity, and cost, many are too insensitive for routine screening. DNA hybridization methods, which are labor-intensive, have proven to yield sensitivities and specificities similar to the antigen-based methods.

The most sensitive means of *Chlamydia* detection so far are the commercially available nucleic acid amplification–based assays, such as polymerase and ligase chain reactions. They are estimated to be 10 to 20% more sensitive than culture. A great advantage is that urine has been shown to be an acceptable specimen for detecting *C trachomatis*. This is a significant advance, especially for testing males, since it makes a urethral swab unnecessary. These assays are more expensive than the antigen detection assays, however. They are also more technically demanding—they require sophisticated equipment and an average of 4–5 hours. Inhibition of the assay has been reported, but future generations of the tests promise to improve on these problems.

In summary, antigen detection methods, while easy to perform and readily available, have low sensitivity. Due to the technical requirements of DNA amplification, the most sensitive method for *Chlamydia* detection, the test is generally not found in small laboratories but in more centralized testing facilities. Culture, due to its variability and tight restrictions of specimen collection and transportation, is impractical for most small laboratories but can be found in large teaching hospitals and reference laboratories.

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Diseases Associated With the Major Histocompatibility Complex

THE MAJOR HISTOCOMPATIBILITY COMPLEX (MHC) is a genetic region that encodes for class I and class II molecules and a variety of other proteins. The class I and class II molecules are human leukocyte antigen (HLA) proteins and are essential for the immune system to recognize and respond to foreign antigens. This region of the genome is diverse, with hundreds of alleles of the different HLA genes. Because of its importance in organ transplantation, the MHC locus has been the focus of many studies; many of the alleles are known. Other than HLA antigens, the MHC encodes for a variety of other proteins including proteins from the complement system and tumor necrosis factor (TNF).

Some HLA alleles have been found to be correlated with specific diseases, so determining a patient's HLA type is useful in diagnosing a disease, diagnosing a variant of a disease, predicting a person's susceptibility to a disease, or predicting the course of a disease. There are several explanations for the predictive value of HLA types. Many infectious and autoimmune diseases are influenced by the immune response. Different HLA types may be associated with differences in immune responses

and may make an individual susceptible or resistant to a particular disease. Also, the MHC region is densely packed with genes, many of which are important for function. Hence, mutations in this region of the genome are more likely to result in a disease than mutations in a region of the genome that has very few coding regions. Furthermore, the MHC region may be a "hot spot" for mutagenesis. Finally, the polymorphic nature of this region means that a mutation in or near the MHC complex is likely associated with a specific HLA type that is not found in many people. Hence, specific HLA types can serve as markers that are linked with defective genes in this region.

While diseases have been known to be correlated with specific HLA loci for some years, recent advances in molecular biology have resulted in the discovery of many more disease associations. Classic serologic techniques define an HLA type by reactivity of an antibody or antisera with HLA molecules. DNA analysis has shown that one classic HLA type can be further subdivided into a set of alleles with slightly different sequences. These alleles are known as subtypes of an HLA type. If a disease is associated with only one particular HLA subtype, then studies employing classic serologic techniques might fail to establish a statistically significant correlation between the disease and HLA markers. In these cases, molecular techniques can determine HLA subtypes and might establish that one HLA subtype is associated with the disease.

HLA studies can help investigators classify diseases. Juvenile rheumatoid arthritis (JRA), for example, can have several presentations. Researchers proposed classifying JRA into various subtypes based on clinical features and then found that different JRA subtypes correspond with different HLA subtypes. This provides evidence that different forms of JRA arise from different pathophysiologic mechanisms and may be responsive to different therapeutic interventions.

Diseases that are associated with specific HLA types or subtypes include ankylosing spondylitis, type 1 diabetes mellitus, Behçet's disease, celiac disease, Grave's disease, Hashimoto's thyroiditis, Hodgkin's disease, idiopathic membranous nephropathy, idiopathic nephrotic syndrome, multiple sclerosis, narcolepsy, C2 deficiency, C4 deficiency, congenital adrenal hyperplasia, idiopathic hemochromatosis, gluten-sensitive enteropathy, pemphigus vulgaris, cicatrical pemphigoid, Goodpasture's syndrome, juvenile rheumatoid arthritis, and rheumatoid arthritis. In addition, susceptibility to malaria infection and rapid or slow progression of HIV infection are associated with specific HLA types.

For most diseases, molecular techniques that determine HLA subtypes provide the most useful information. These studies can be complicated, however, because in some diseases, such as type 1 diabetes, certain HLA subtypes (DQA1*0301, for example) are associated with an increased risk of contracting the disease but other subtypes (DQA1*0102, for example) are associated with a decreased risk of contracting the disease.

Some of the diseases with the strongest associations with specific HLA genotypes in the general population are ankylosing spondylitis, narcolepsy, and celiac disease. HLA typing can be useful in many other diseases, however. Often when a family member has a disease, the family and physician want to know the likelihood that other family members will develop the disease. In these cases, comparing the HLA type of the proband with relatives can provide useful information even if the disease does not have a strong correlation with particular HLA subtypes in the general population. Also, in specific clinical situations, HLA testing may help refine a differential diagnosis or predict the progression of an illness.

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Kaposi's Sarcoma–Associated Herpesvirus (KSHV): A New Viral Pathogen Associated With Kaposi's Sarcoma, Primary Effusion Lymphoma, and Multicentric Castleman's Disease

KAPOSI'S SARCOMA–ASSOCIATED HERPESVIRUS (KSHV), also known as human herpesvirus 8 (HHV-8), is a member of the gammaherpesvirinae subfamily of herpesvirus that are characterized by the ability to replicate in lymphoblastoid cells. KSHV is related to Epstein-Barr virus (EBV) and herpesvirus saimiri (HVS) and is the first member of the genus *Rhadinovirus* known to infect humans. Viral DNA was first discovered in Kaposi's sarcoma lesions by Chang and Moore, who used representational difference analysis to identify KS330Bam and KS631Bam fragments. As shown by ELISA for HHV-8 antibody, the prevalence of KSHV is much lower than other human herpes viruses (EBV, HHV-6, cytomegalovirus, herpes simplex virus 1). Less than 20% of normal adult donors and 33% of HIV-negative homosexual men have antibodies to KSHV. Both HIV-positive and -negative patients with Kaposi's sarcoma have antibodies to KSHV (titer >1280 in most cases), and seroconversion has been documented before the development of Kaposi's sarcoma. KSHV also is now known to be associated with a new lymphoma subtype, primary effusion lymphoma, and with lymphoid proliferations resembling angioimmunoblastic lymphadenopathy with dysproteinemia (AILD) and multicentric Castleman's disease.

Primary effusion lymphoma occurs predominantly in HIV-infected male patients; the primary symptom is lym-

phomatous effusions (pleural, pericardial, or ascitic) without a contiguous tumor mass. Primary effusion lymphomas mainly occur in older patients (most in the fourth decade of life) and with more advanced disease than Burkitt-like lymphomas. The patients are usually severely immunosuppressed (T cells <100/mm^3), and most have prior manifestations of AIDS, including opportunistic infections. Morphologically, the tumors resemble B cell immunoblastic and large-cell anaplastic lymphomas. In most patients, disease is limited to body cavities, but occasional cases have involved adjacent organs such as the lung, soft tissues, regional nodes, and bone marrow. KSHV-associated lymphomas have also been identified in the central nervous system and the gastrointestinal tract, in HIV-negative men, and in women. The prognosis is poor, and the majority of patients die within 1 year of diagnosis.

Phenotypically, primary effusion lymphomas express leukocyte common antigen (CD45), but most are negative for other B and T cell–associated antigens including CD20, CD19, and immunoglobulins. The cells have activation antigens including HLA-DR and CD30. Molecular analysis confirms derivation from late differentiating B cells, possibly at the immunoblast, plasmablast, or preplasma cell stage. Herpesvirus particles consisting of 100- to 115-nm capsids with central cores have been identified within neoplastic cells. Most cases in HIV-seropositive individuals are also positive for EBV (type A or B). Unlike most EBV-associated lymphomas, however, there appears to be no involvement of c-*myc*. They also lack *bcl-6* gene rearrangements and *ras* oncogene or *p53* tumor suppressor gene mutations. Cytogenetic studies reveal multiple chromosomal abnormalities. Preliminary data suggest that involvement of two potential oncogenes, one a cellular type D cyclin similar to the PRAD 1 oncogene involved in mantle cell lymphomas, and one homologous to the cellular G protein–coupled receptor (GCR) family of proteins. The virus contains proteins similar to human macrophage inflammatory protein (MIP) chemokines and interleukin-6 (viral IL-6), which may play a role in the pathogenesis and clinical syndrome of multicentric Castleman's disease.

KSHV has been associated with benign lymphoid proliferations from HIV-positive and -negative patients with AILD and multicentric Castleman's disease. KSHV is present in almost all cases of Castleman's disease in patients with AIDS and in approximately half the cases in HIV-seronegative patients. KSHV sequences have also been detected in peripheral blood lymphocytes from patients with Castleman's disease. Multicentric Castleman's disease occurs most often in older patients, predominantly men, and is associated with lymphadenopathy and constitutional symptoms. We have detected KSHV sequences in a child with familial multicentric Castleman's disease, and other children have been seropositive for KSHV. Patients with Castleman's disease may develop secondary malignancies, most commonly Kaposi's sarcoma and non-Hodgkin's lymphoma. In HIV-infected patients with Castleman's disease, there is a strong association between KSHV and sexual transmission, as well as the development of Kaposi's sarcoma.

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Cocaethylene: A Novel Cocaine Homolog

COCAETHYLENE (CE) is a pharmacologically significant homolog of cocaine, formed by transesterification of cocaine with ethanol when the two are ingested concurrently. This reaction is mediated by a hepatic carboxylase which, in the absence of ethanol, catalyzes the production of benzoylecgonine, the major urinary metabolite of cocaine.

As is the case for cocaine, CE binds to the dopamine transporter and inhibits dopamine uptake into synaptosomes. The behavioral pharmacology as well as the psychomotor stimulant effects of CE are similar to those of cocaine, but the toxicity of CE is greater than that of cocaine, and its LD_{50} is much lower. Furthermore, the plasma half-life of CE in humans is longer than that of cocaine, and plasma concentrations of CE often exceed those of cocaine itself. Taken together, these factors make CE a compound of toxicological importance.

Recent work has demonstrated that CE binds with high affinity to human serum alpha-1 acid glycoprotein (orosomucoid) and with low affinity to serum albumin. Human brain, heart, liver, and placenta also bind both cocaine and CE.

Both cocaine and CE can be quantitated simultaneously in plasma and urine by high-pressure liquid chromatography. Thin-layer chromatography of urine is useful for the qualitative detection of cocaine and CE if a solvent system consisting of hexane (65 ml):toluene (20 ml):diethylamine (5 ml) is used. Both compounds can be readily visualized as reddish-brown spots after the plate is sprayed with iodoplatinate (cocaine, R_f 0.44; CE, R_f 0.51). Furthermore, both are metabolized to benzoylec-

gonine, which can be easily detected by qualitative immunoassay of the urine.

While not likely to be encountered clinically, the isopropyl and propyl homologs of cocaine (cocaisopropylene and cocapropylene) have also been described, and their formation has been demonstrated by incubation of human liver homogenates with isopropanol and *n*-propanol, respectively. These compounds, if present in urine, can be detected by thin-layer chromatography.

Detection of CE and other cocaine homologs is clinically important since their presence may help explain persistence of drug effects after the parent drug has dissipated.

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Alerts, Notices, and Case Reports

AIDS-Related Lymphomas With Neurologic Manifestations

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THE ASSOCIATION OF HIV INFECTION with lymphoma is well documented, with an increasing incidence of lymphoma in the late, symptomatic stage of AIDS. Approximately 3 to 5% of HIV patients will be affected, a rate 60 to 100 times greater than in the general population.[1-4] The presenting manifestation and late complications of HIV-associated lymphoma may be neurological. We present four cases of AIDS-related lymphoma with prominent neurological features to heighten the awareness of physicians managing patients with HIV infections and neurological abnormalities.

Case 1: AIDS-Related Lymphoma and Confusion

A 28-year-old Caucasian man presented with a one-week history of amnesia, loss of direction, and vague confusion. He had contracted HIV 8 years before from a blood transfusion at the time of cardiac transplantation for congenital myopathy. Because of the cardiac transplantation, he had remained on imuran and prednisone. Two years before his terminal illness, his CD count was 104/cm^3. During his last two years of life, he was treated with AZT and his course was complicated by myopathy, confirmed by EMG of his thighs.

Examination at the time of mental confusion revealed hyporeflexia of all extremities with downgoing plantar responses on Babinski's testing. A CT scan with contrast revealed three ring-enhancing masses in the left frontal, left occipital, and left temporal areas (Figure 1). Despite treatment with pyrimethamine and sulfisoxasole, the patient continued to deteriorate, with periodic vomiting. A brain biopsy performed stereotactically with computerized tomography (CT) guidance revealed a large-cell immunoblastic lymphoma (LCIBL) with special immunostainings revealing a large number of L-26 cytoplasmic membrane positive immunostaining cells. Only a small number of tumor cells showed weak, vague staining for BER-H2 immunostains, and the tumor cells were all negative for UCHL-1, MAK387, and cytokeratins. His Epstein-Barr virus (EBV) IgG was strongly positive. The patient elected to be managed symptomatically and died 2 weeks later.

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Figure 1.—CT scan with contrast of head with a ring-enhancing lesion in the white matter.

Case 2: AIDS-Related Lymphoma of the Peripheral Nervous System and the Central Nervous System

A 45-year-old Caucasian man had a past history of transverse myelitis and positive EBV titer. He was found to be HIV positive in May 1987. Zidovudine was given initially, and later didanosine was added for antiretroviral therapy. In 1994, a biopsy from a rapidly enlarging axillary lymph node revealed a LCIBL. One month after cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) chemotherapy he returned with numbness of his chin. The chemotherapy was continued and the numbness resolved 2 weeks after onset. Three months after initial tumor regression, the patient had a central nervous system (CNS) relapse with spinal cord compression and right facial nerve paralysis. He died 1 month after the relapse.

Case 3: AIDS-Related Lymphoma and Mental Neuropathy

A 27-year-old Caucasian woman came to the emergency department with a 1-month history of left-sided neck mass, a 2-day history of horizontal diplopia and bilateral paresthesias, and numbness of her chin and lower lip. Examination demonstrated a right-sided sixth nerve palsy and bilateral mental neuropathy. Magnetic resonance imaging (MRI) of the head showed an enhancing soft tissue thickening of the falx (Figure 2). A CT scan of the neck revealed bilateral cervical lymphadenopathy (Figure 3). HIV and EBV IgG serologies were positive. Lymph node biopsy revealed small non-cleaved cell lymphoma (SNCCL). Treatment with systemic chemotherapy, consisting of a low-dose modification of methotrexate,

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
ALCL = anaplastic large-cell lymphoma
CNS = central nervous system
CSF = cerebrospinal fluid
CT = computerized tomography
DLCL = diffuse large-cell lymphoma
EBV = Epstein-Barr virus
HIV = human immunodeficiency virus
IL = interleukin
LCIBL = large-cell immunoblastic lymphoma
LNCCL = large non-cleaved cell lymphoma
MRI = magnetic resonance imaging
SNCCL = small non-cleaved cell lymphoma

bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone regimen (m-BACOD), and intrathecal cystosine arabinoside resulted in temporary resolution of the mental neuropathy. Despite this, the patient died of recurrent lymphoma 6 weeks after presentation, before cranial irradiation could be given.

Case 4: AIDS-Related Lymphoma and Sciatica

A 49-year-old Caucasian man had been diagnosed with HIV infection 6 years before an enlarging right-sided axillary lymphadenopathy. The patient had chronic lymphadenopathy in multiple lymph node bearing areas and had been treated with zidovudine and zalcitabine. His serology was also positive for prior exposure to EBV.

He developed chills and fever and enlarging lymph nodes in the right axillary area, which on biopsy revealed a SNCCL. Three months later, he developed severe burning pain radiating down into the right buttocks and into the right thigh, extending to the lateral aspect of the right foot. A CT scan revealed a swollen right psoas muscle with an irregular mass 4 to 5 cm, close to the anterior margin of the pelvic bone. In addition, there was right lateral sacral wing infiltration into the soft tissues consistent with recurrent lymphoma (Figure 4). Despite radiation therapy, the patient developed a foot drop as the lymphoma progressed. He was discharged with hospice care and died 5 months after the initial diagnosis of lymphoma.

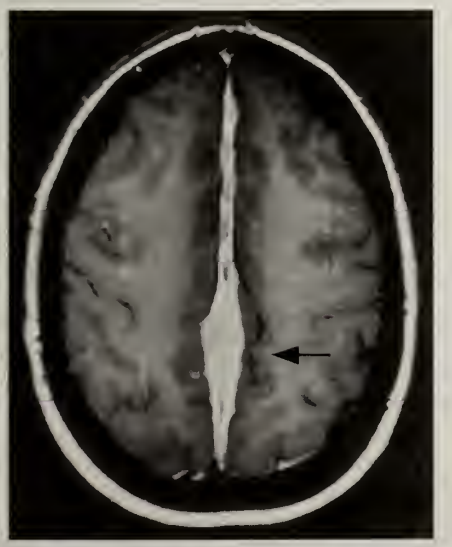

Figure 2.—Coronal T-1 weighted MRI of the head with contrast showing enhanced soft tissue thickening of the falx.

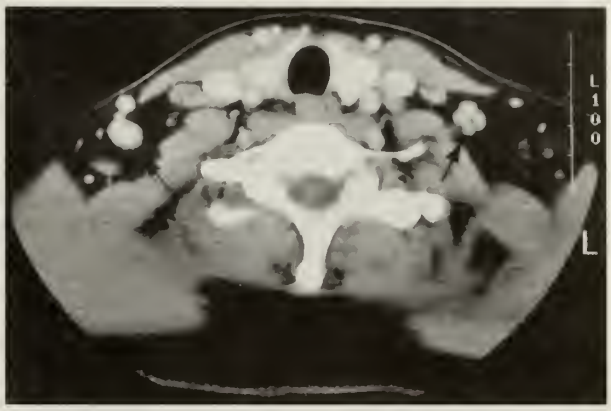

Figure 3.—CT of the head and neck demonstrating extensive cervical lymphadenopathy.

Discussion

Overview of AIDS-Related Lymphomas

AIDS-associated lymphomas are overwhelmingly derived from B cells and occur as either primary CNS or systemic disease.[1-4] Of the AIDS-related lymphomas, 80 to 90% are intermediate or high grade non-Hodgkin's lymphoma, in contrast to the 10 to 15% found in the general population.[1-4] The majority are either diffuse large-cell lymphoma (DLCL) or SNCCL.[1-6] DLCL, according to a recent consensus statement, includes the Working Formulation classifications of large non-cleaved cell lymphoma (LNCCL), LCIBL, and anaplastic large-cell lymphoma (ALCL).[7,8] SNCCL is a Working Formulation category with the subtypes Burkitt's and non-Burkitt's (Table 1).

Primary CNS lymphoma is a rare neoplasm, which was first seen with an increased incidence in chronically immunosuppressed patients such as those who had under-

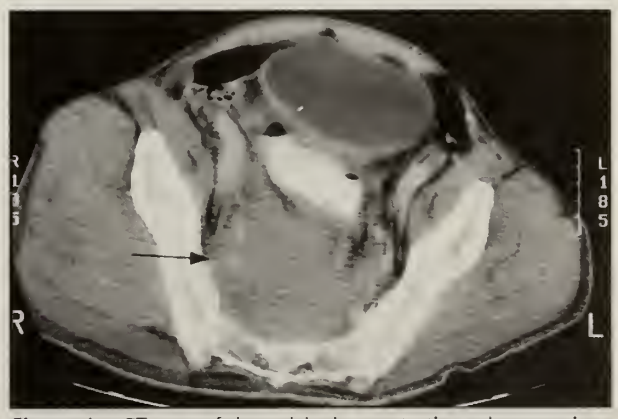

Figure 4.—CT scan of the pelvis demonstrating a large perirectal mass.

Table 1.—*AIDS-Related Lymphomas*

Primary CNS Lymphoma
• Diffuse large cell lymphoma (72%)*
• Small non-cleaved cell lymphoma (25%)
Systemic Lymphoma
• Small non-cleaved cell lymphoma (80–90%)
• Diffuse large cell lymphoma
Body Cavity–Based Lymphomas

*DLCL includes the Working Formulation classifications of large non-cleaved cell lymphoma (LNCCL), large cell immunoblastic lymphoma (LCIBL), and anaplastic large cell lymphoma (CLCL).[3,8]

gone renal transplantation.[5] Although it has been noted that the frequency of this neoplasm is increasing in the general population, there is an incidence of 2 to 6% of primary CNS lymphoma in AIDS patients,[5] approximately 60-fold greater than in the general population. It is the second most common CNS mass lesion in AIDS patients, after toxoplasma.[5,6,9]

In approximately 72% of cases, the primary CNS lymphoma in AIDS is a DLCL,[1,5] and 25% are SNCCL.[5] Primary CNS lymphoma is defined as limited to the cranial-spinal axis without systemic disease. In contrast, 80 to 90% of systemic lymphomas are SNCCL.[1,3] The remainder of systemic lymphomas are mostly DLCL.[1] The CNS can be secondarily involved in both types of systemic lymphomas. The prognosis of these AIDS-related lymphomas is poor, despite intensive chemotherapy, with a median survival of 2 to 4 months for primary CNS disease and 4 to 6 months for peripheral lymphoma. Moreover, patients with primary CNS lymphoma have a more advanced HIV infection, with CD4 counts averaging 40/mm^3, compared with average counts of 190/mm^3 found with peripheral lymphomas.[1,4] The different prognosis is probably related to the site of the disease rather than the predominance of DLCL with the CNS disease. This is supported by the observation that the prognosis is as good if not better for patients with systemic DLCL when compared to patients with systemic SNCCL.[1]

Another AIDS-related non-Hodgkin's lymphoma is the unique body cavity–based lymphoma.[10] These are uncommon AIDS-related B cell lymphomas which grow in the pleural, pericardial, and peritoneal cavities and have indeterminate immunophenotypes.

Although other types of lymphomas can occur with AIDS, both Hodgkin's and non-Hodgkin's, they do not occur with increased frequency in AIDS patients and are consequently not considered to be AIDS-related.[1,2]

Pathogenesis of AIDS-Related Lymphomas

It is clear that the AIDS-associated lymphomas are heterogeneous and that multiple mechanisms are involved in the pathogenesis.[2,7] Epstein-Barr virus infection has been implicated in the genesis of some lymphomas associated with AIDS as well as the increased incidence of B cell lymphomas in other settings of altered immune function, such as transplantation and autoimmune diseases.[2,3,7] Supportive etiopathologic evidence in these instances includes the observed immunologic defects which selectively impair immunosurveillance against EBV-infected B cells, permitting an ongoing reactive proliferation of B cells. EBV is also commonly reactivated in AIDS patients and has been associated with the progression of persistent generalized lymphadenopathy to lymphoma and also with the extranodal presentation of lymphomas.[2,7] The finding that the EBV DNA in the lymphomas is clonal suggests that the EBV infection of the B cells occurs before the clonal expansion.[2]

EBV infection does not cause a full malignant transformation. It is therefore hypothesized that although the EBV immortalizes the B cells, genetic mutations are also required to cause malignant transformation.[2,7] Abberration of the c-MYC gene with a translocation of the 8Q24 to the 14Q32, an area near the heavy chain immunoglobulin genes, has been identified in some EBV-related lymphomas as well as AIDS-related lymphomas not associated with EBV infection. The c-MYC gene has been implicated in EBV lymphomagenesis by causing alterations of cellular functions that may be positively selected in the context of immunodeficiency. Examples include downregulation of the LFA antigens involved in cell conjugate formation between B cells and cytotoxic T cells, NK cells, and vascular endothelia.[7]

The rate of isolation of EBV particles from AIDS-related lymphoma is 80 to 100% in AIDS-related DLCL, but only 30% in AIDS-related SNCCL.[1,7] AIDS-related DLCL expresses the EBV-related particles EBNA-2 and latent membrane protein-1 (LMP-1); SNCCL does not.[3,7] It is interesting to note that LMP-1 has transforming and oncogenic properties.[3] It is therefore apparent that EBV infection is not etiologic in all AIDS-related lymphomas. A range of genetic abnormalities has been identified to help partly explain the oncogenesis of AIDS-related lymphomas.[3] The dysregulation of the dominantly acting c-MYC oncogene has been found in 100% of AIDS-related SNCCL and only 20% of AIDS-related DLCL.[7] In contrast, BCL-6 rearrangements are found in 20% of AIDS-related DLCL and have not yet been found in AIDS-related SNCCL.[7] Furthermore, inactivation of the tumor suppressor locus *p53* is found in 60% of AIDS-related SNCCL and rarely in AIDS-related DLCL.

Other possible causative factors include the finding that AIDS-related SNCCLs produce antibodies against self-antigens. This suggests that B-cell clonal selection is driven by this and is involved in lymphomagenesis. Furthermore, deregulation of the cytokines interleukin (IL)-6 and -10 has uniquely been associated with the development of AIDS-related lymphomas.[7]

More recently, researchers[10] have found that DNA sequences of the Kaposi's sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus-8 (HHV8), are found not only in Kaposi's sarcoma but also in the rare AIDS-related body cavity–based lymphomas. Unlike the other systemic AIDS-related lymphomas, these frequently contain EBV and consistently have no rearrangements of the c-MYC gene. The KSHV sequence is not

found in other AIDS-related and non-AIDS-related lymphomas. Furthermore, its occurrence with this unique tumor supports the possibility that another infectious agent may be associated with the development of lymphoma.

Lymphomas and Neurologic Abnormalities

The neurologic abnormalities associated with HIV infection may involve any part of the brain (Case 1), spinal cord (Case 2), and peripheral nervous system (Cases 2, 3, and 4) and result from a diverse range of causes.[11]

Case 1, a primary CNS AIDS-related DLCL, highlights the fact that lymphomas may present with an alteration of mental status without focal features. Fine et al.[5] noted that 51% of patients with AIDS-related primary CNS lymphoma presented with neurologic deficits, 53% with mental status changes, 26% with seizures, and 14% with increased intracranial pressure. The challenge with primary CNS lymphomas in AIDS patients is differentiating them from toxoplasma.[5] With CNS imaging, the primary CNS lymphomas are often single or few in numbers, commonly located (as in Case 1) in the hemispheric white matter, contrasting with the more frequent multiple lesions of toxoplasmosis which are slightly more commonly found adjacent to or within gray matter including the deeper structures of the brain.[12] Interestingly, 52% of AIDS-related primary CNS lymphomas show some degree of ring enhancement, but this has not been seen in primary CNS lymphomas in immunocompetent hosts. However, the radiographic differences between toxoplasma and primary CNS lymphoma are not great enough to be diagnostic,[12] and a stereotactic guided biopsy for the diagnosis after a failed empiric trial of therapy against toxoplasmosis is frequently required. Histologically, toxoplasmosis is diagnosed by identifying tachyzoites with immunofluorescent antibody or peroxidase-antiperoxidase immunohistochemical techniques.[13] However, if the toxoplasma organisms cannot be identified, routine stains cannot easily differentiate toxoplasmosis from lymphoma. Therefore, when in doubt, special stains for lymphocyte types can be done or flow cytometry can be used, which demonstrates a monoclonal cell line, as in Case 1. Toxoplasma lesions have a mixed lymphocyte cellularity. Research efforts are currently evaluating the sensitivity and specificity of tumor markers in the cerebrospinal fluid (CSF). The detection of EBV DNA from CSF by nested polymerase chain reaction has shown some promise.[14]

Case 2 developed terminal spinal cord compression, after an initial mental nerve dysfunction. The latter is an example of a peripheral neuropathy associated with a lymphoma and can be caused by various mechanisms.[15] Vasa nervorum vasculitis and paraneoplastic syndromes such as a peripheral sensorimotor neuropathy with axonal degeneration without lymphomatous infiltrates may occur. Direct involvement of the neural tissue has been seen with invasion of the nerve by lymphomatous cells as in Case 3, or the neuropathy may be caused by direct compression from the adjacent lymph nodes or osseous involvement. Case 4 exemplifies this.

Cranial nerve palsies are known to occur with malignancies including lymphoma.[16–19] An incidence of 1.2% for lymphoma and leukemia has previously been reported.[18] Cases 2 and 3 both had a mental neuropathy (details published elsewhere).[20] Mental neuropathy has been considered to be the hallmark of a highly aggressive and rapidly progressive lymphoma, although it is rarely associated with benign conditions.[16,18,19] It has only once before been reported in a patient with an AIDS-related lymphoma.[21] The mental nerve is one of the terminal branches of the mandibular division of the trigeminal nerve. The inferior alveolar nerve traverses the mandible in a diffuse plexiform manner and emerges from the mental foramen as the mental nerve. Mental neuropathy is perceived as numbness and/or paresthesias of the skin of the chin, lower lip, and buccal surface of the lower lip. Although initial studies may not find a cause for a mental neuropathy in patients with a history of malignant disease, it has been observed that malignant disease may become manifest months later.[19] Moreover, the fact that radiation to the mandible without brain irradiation has been shown to resolve the nerve dysfunction indicates that the neuropathy may be due to lymphomatous involvement of the mandible with CNS disease being coincidental.[19]

With the increasing number of HIV-infected patients and AIDS-related lymphomas, the clinician should be vigilant for clues to help identify patients with complications of the virus. These four cases highlight how AIDS-related lymphomas may involve any part of the nervous system, and therefore, neurological abnormalities may herald the presence of lymphoma or develop from the late complications of these aggressive malignancies.

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Wegener Granulomatosis Causing Sellar Mass, Hydrocephalus, and Global Pituitary Failure

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IN A SINGLE CASE we found several unusual or difficult features of Wegener granulomatosis. First, Wegener can attack the sella, causing anterior and posterior pituitary failure, hemianopsia, and hydrocephalus. Second, ventriculo-peritoneal shunting can worsen chiasmal compression due to the Wegener sellar mass. Third, extensive and severely active Wegener may be negative for antibodies to neutrophil cytoplasm. Fourth, the long-term management of Wegener, often dependent on nonspecific signals such as the sedimentation rate and C-reactive protein (CRP), is especially difficult with critical central nervous system lesions. Fifth, monthly intravenous cyclophosphamide (CTX) is not as effective as daily oral CTX in severe cases of Wegener. Sixth, dapsone and biweekly oral CTX independently may be useful in long-term management of Wegener. Finally, neurosurgical and medical therapy can bring about an enduring remission even in this severe form of Wegener.

Report of a Case

In June 1989, a 36-year-old woman developed frontal headaches, rhinorrhea, epistaxis, anosmia, amenorrhea, and weight loss. Examination in late July showed a cushingoid appearance, tenderness of the left maxillary sinus, reduced pubic hair, and reduced olfaction. The chest x-ray showed multiple irregular nodules in both lung fields. The Westergren erythrocyte sedimentation rate (ESR) was 115. The morning cortisol was 29 μg/ml (normal range 4.3–29 μg/ml). The luteinizing hormone response to gonadotrophic releasing hormone and the thyroid stimulating hormone response to thyrotropin releasing hormone were blunted. A magnetic resonance image of the head revealed a large macrocystic pituitary tumor with suprasellar extension and hydrocephalus. There was hemorrhage along the falx and corpus cavernosum. Urinalysis, urinary protein excretion, and creatinine were normal. Anti-neutrophil cytoplasm antibodies (ANCA) were absent at 2 and 5 months after illness onset.

In early August, the patient developed focal left seizures and weakness. Lumbar puncture showed an opening pressure of 204 mm water, a protein of 65, and 45 lymphocytes/mm^3. In mid-August, severe bilateral conjunctivitis, left external otitis, and increasing sinus pain developed. A nasal mucosa biopsy showed Wegener granulomatosis. Prednisone 60 mg daily and replacement doses of thyroxine and estrogen were started. CTX 865 mg was infused IV.

The symptoms improved dramatically, with persistence only of headache. The pulmonary infiltrates vanished. Prednisone was reduced to 20 mg twice daily. CTX was infused IV on October 3 (750 mg) and November 3 (1.25 gm). The headaches worsened, however, and visual field monitoring showed bitemporal scotomata by November 10. A repeat magnetic resonance image of the head revealed no change in the sellar mass. Computed tomography of the head showed generalized hydrocephalus. Lumbar puncture showed an opening pressure of 180 mm water, a protein of 96, 190 lymphocytes/mm^3, and 20 granulocytes/mm^3. The patient underwent a ventriculo-peritoneal shunt on November 27. Her headaches subsided, but her visual field defects sharply enlarged. On December 7, a transnasal transsphenoidal resection of the pituitary lesion was performed. The histology showed Wegener granulomatosis. A single grand mal seizure following the procedure was treated with phenytoin without recurrence. Diabetes insipidus became apparent in the immediate postoperative period; intranasal desmopressin acetate was ineffective, presumably due to poor absorption, but subcutaneous desmopressin acetate reversed the hyponitremia.

A week following surgery, CTX 150 mg orally daily and trimethoprim/sulfamethoxizole (T/S), one daily, were started. Prednisone was reduced to 17.5 mg in the morning and 2.5 mg in the evening. This corticosteroid dose was gradually reduced to replacement levels over the next 6 months.

The patient's visual fields normalized rapidly. In late December she developed a shunt infection due to *Pseudomonas aeruginosa*, successfully treated with shunt replacement and vancomycin, ceftazidime, and metronidazole. By mid-January 1990, the patient was asymptomatic except for hair loss attributable to oral CTX. Daily oral CTX was continued for 6 months postoperatively, adjusted to mild granulocytopenia. At this point, her acute phase reactants reached their nadir (Figure 1). In an effort

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ABBREVIATIONS USED IN TEXT

AGC = absolute granulocyte count
ANCA = anti-neutrophil cytoplasm antibodies
CRP = C-reactive protein
CTX = cyclophosphamide
ESR = erythrocyte sedimentation rate
T/S = trimethoprim/sulfamethoxizole

to reduce the morbidity of long-term oral CTX, monthly intravenous CTX was started 7 months postoperatively, following a month off oral CTX. During four successive months the patient received an initial dose of 0.75 g/m^2, followed by three doses of 1 g/m^2. The ESR, CRP, and granulocyte counts all sharply increased. Because of these trends, oral CTX was restarted and adjusted to 125 mg daily (Figure 1).

Over the next year, the acute phase reactants remained consistently moderately elevated. Exchanging T/S for dapsone 100 mg daily resulted in a marked decline in ESR and CRP, which was maintained for at least 4 months after the CTX dose was reduced to 50 mg daily (Figure 2). Two years later, because of increasing ESR and CRP, CTX was changed to 250 mg twice weekly with fluid diuresis on dosage days. The acute phase reactants showed further decline. Six years following hypophysectomy, the patient remained asymptomatic on multiple hormone replacements, dapsone, and CTX 150 mg twice weekly. She was able to switch to intranasal desmopressin acetate.

Discussion

Sellar invasion by Wegener granuloma is rare.[1,2] This case was also unusual in the absence of both cellular urinary sediment and ANCA.[3] It is likely that these negatives delayed the diagnosis of Wegener. A recent meta-analysis showed that >90% of active cases of Wegener are positive for ANCA.[4] This statistic exaggerates the sensitivity of ANCA because it applies only to well-established and mostly biopsy-proven cases. Before diagnosis, ANCA may be negative in 50 to 70% of Wegener cases.[5,6] Given the wealth of findings aside from the sellar mass—sinusitis, otitis, rhinitis, epistaxis, conjunctivitis, and nodular pulmonary infiltrates, which are all uniquely within the spectrum of Wegener,[3,7,8]—a more timely diagnosis of Wegener should have been made. The dramatic, albeit partial, response to corticosteroids was confirmatory. The histopathology of the nasal mucosa, and later of the sellar mass, proved a diagnosis that was nearly certain on clinical grounds.

One begins the treatment of Wegener with confidence that daily CTX will prevent progressive tissue damage and death.[3] The role of pulse intravenous CTX in Wegener was little studied before 1989, but its advantages over oral CTX in systemic lupus suggested unique utility in Wegener. In this case, the choice of therapy was critical because of the invasion of the sella and the optic chiasm by granuloma. The original choice of fairly modest intravenous pulses of CTX and high-dose corticosteroid was made at another center. The patient went to surgery for hydrocephalus and an expanding sellar granuloma having received 14 weeks of high-dose prednisone and three intravenous boluses of CTX totaling 2.865 grams.

Decompression of the hydrocephalus was a priority because of incapacitating headache, but the post-shunting worsening of visual field defects almost certainly was due

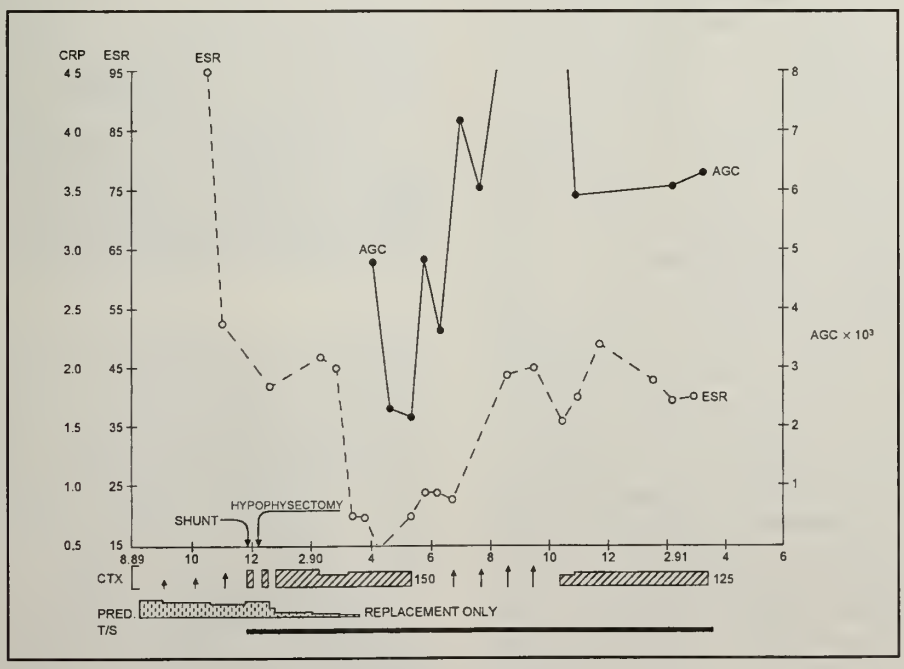

Figure 1. Course of absolute granulocyte count (**AGC**) and erythrocyte sedimentation rate (**ESR**) over the first 8 months. AGC and ESR increased sharply upon switch from daily oral cyclophosphamide (**CTX**, shaded boxes) to IV pulse **CTX** (vertical arrows). Pred. = prednisone. T/S = trimethoprim/sulfamethoxizole.

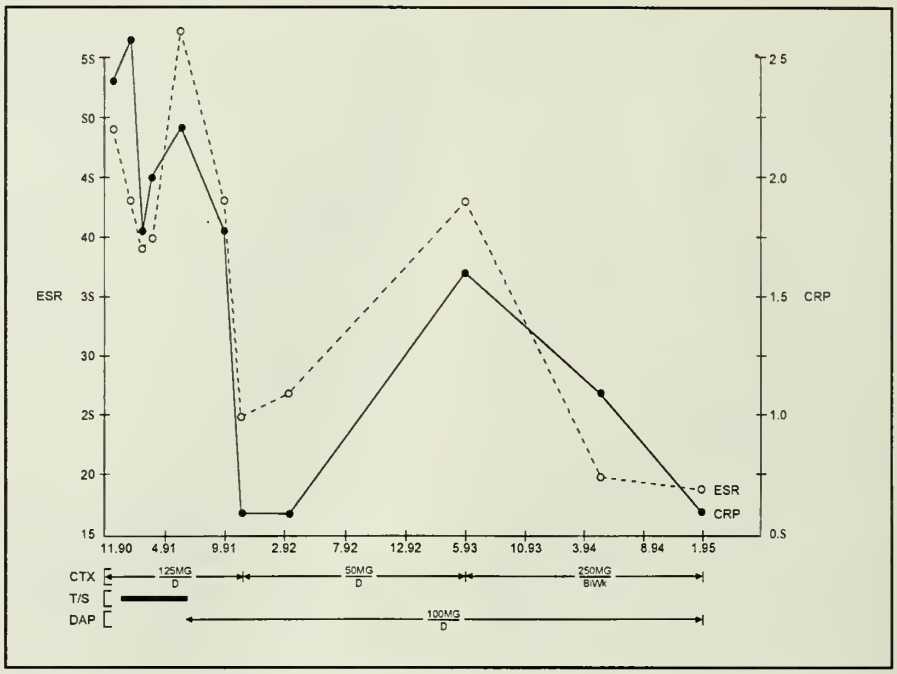

Figure 2. Course of **ESR** and C-reactive protein (**CRP**) during maintenance therapy. Dap = dapsone.

to expansion of the inflammatory mass in the sella. Therefore priority should have been placed on excising the Wegener mass. Following the neurosurgical procedures, the patient received oral CTX 150 mg daily and T/S with striking improvement over 5 months in clinical status and acute-phase proteins, associated with mild granulocytopenia.

With the remarkable success of the neurosurgical intervention and initial medical therapy, the challenge became the successful management of Wegener without measurable target organ effects. ANCA was absent; in any event it is of modest utility in following Wegener.[9] At no time did the patient have abnormal renal sediment or renal dysfunction. The pulmonary granulomas present at the outset subsided after initial therapy. At 2 months following surgery, even her mild residual headaches had vanished, leaving an asymptomatic patient.

The management of Wegener often spans decades. While the medium-term outcome of oral CTX therapy is good, damage to or carcinogenesis of the bladder is a well-documented problem. T/S has proven an effective adjunct in controlling Wegener,[10–12] and a rationale for the use of sulfonamides, including dapsone, as anti-inflammatory agents in Wegener has been advanced.[13] However, this is the first report of the use of dapsone in Wegener. Another approach to reducing CTX toxicity has been to administer it in IV pulses, with fluid diuresis.[14,15] Here IV CTX failed twice, first as an initial therapy at 0.5–0.75 g/m^2, then as maintenance therapy at 1.0 g/m^2, as assessed over 3- to 4-month intervals. This failure is consistent with the work of Reinhold-Keller showing that IV CTX maintained remission in only 42% of Wegener patients; extensive disease and positivity for ANCA predicted lower success rates.[15]

It is common clinical wisdom that the ESR and CRP reflect the activity of Wegener. In this case, the strong correlation between these tests and their consistency in the steady state suggests, but of course does not prove, that they mirrored Wegener activity. The substitution of dapsone for T/S resulted in a sharp decline in ESR and CRP first seen after 5 months and sustained for at least another 4 months. Later, the substitution of biweekly oral CTX 250 mg, with fluid diuresis on dosage days to reduce the risk of cystitis, showed advantages over daily CTX 50 mg in reducing the ESR and CRP.

The chief concerns in the long-term management of Wegener are shifting from controlling the disease to controlling the toxicity of treatment. Innovative approaches, such as the use of methotrexate,[11] intermittent oral CTX, or dapsone, must be validated by long-term cooperative studies.

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An Anterior Mediastinal Mass With Draining Sternal Sinus Tracts Due to *Nocardia braziliensis*

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THE COMMON DIFFERENTIAL DIAGNOSIS for mass lesions in the anterior mediastinum includes thymoma, Hodgkin's disease, thyroid goiter, parathyroid cyst, germ cell tumors (teratoma, seminoma, choriocarcinoma, embryonal cell carcinoma), and mesenchymal tumors (lipomas, fibromas, mesotheliomas, lymphangiomas).[1] We report an unusual patient with *Nocardia braziliensis* infection who presented with subcutaneous and cutaneous lesions involving the anterior chest wall which extended into the mediastinum.

Report of a Case

A 21-year-old Mexican man came to our emergency department complaining of draining sores on the front of his chest. Approximately 6 months before, he noted a draining lesion on his sternum. The lesion began as a subcutaneous mass that became inflamed and ruptured and initially drained pus. Since then, the number of lesions increased to three and the drainage changed to bloody yellow fluid. He had occasional fevers, chills, and night sweats for the first month only. He denied dyspnea or hemoptysis. There was no history of trauma to the chest wall, but he smoked 1/2 pack of cigarettes per day. The patient noted a decreased appetite and he had lost 23 kilograms since developing these lesions. He applied topical gentian violet to the draining lesions as prescribed by a physician in Mexico. The patient emigrated to the United States from Mexico in 1993, but he returned there 2 to 3 times per year to visit family. The patient worked loading and unloading trucks carrying wooden crates filled with fruits and vegetables. He denied HIV risk factors.

Physical exam revealed a comfortable young man with a temperature of 37°C, blood pressure 114/60, pulse 90 beats/minute, and respiratory rate 12 breaths/minute. There was no peripheral adenopathy. There were three cutaneous ulcerations over his sternum draining serosanguinous fluid (Figure 1). The right anterior chest was swollen compared to the left side and there was a large mass palpable under the right pectoral muscle. The lungs were clear to auscultation and percussion. The cardiac exam revealed regular rate and rhythm with no murmurs, gallops, or rubs. The abdominal exam revealed normal bowel sounds with no masses or hepatosplenomegaly. The extremities showed no cyanosis, clubbing, or edema.

Laboratory studies showed a WBC count of $9.0 \times 10^9/l$ ($9{,}000/mm^3$) with 56.4% neutrophils, 22.3% lymphocytes, 11.9% monocytes, and 9.0% eosinophils. The hematocrit was 0.43 (43%) and the platelet count was $368 \times 10^9/l$ ($368{,}000/mm^3$). The erythrocyte sedimentation rate was 40 mm/hour. Serum electrolytes, transaminases, and blood coagulation studies were normal. The rapid plasma reagent and antibody to HIV were negative. A PPD skin test was negative with a positive mumps control.

A posterioanterior chest radiograph showed a widened mediastinum, and the lateral view showed a soft tissue density just posterior to the sternum. A chest CT scan showed an anterior mediastinal mass which abutted the ascending aorta and the great vessels without vascular encasement. This mass extended to the chest wall and involved the right pectoral muscle (Figure 2). The initial differential diagnosis included lymphoma, primary germ cell tumor, fungal infection, and tuberculosis.

The patient underwent two CT-guided fine needle aspirates of the pectoral and anterior mediastinal mass. The aspirated material was cytologically negative for malignancy and was unremarkable on stain/culture for acid-fast bacilli, fungi, and anaerobic bacteria. Cultures obtained from these aspirates grew branching gram positive rods identified as *Nocardia braziliensis* which was sensitive to trimethoprim/sulfamethoxazole and amoxicillin/clavulanate. Treatment was initiated with trimethoprim/sulfamethoxazole and the patient returned to Mexico.

Discussion

Nocardia are aerobic gram-positive filamentous bacteria which are ubiquitous in soil and are partly respon-

(Kroe DM, Shulman N, Kirsch CM, Wehner JH. An anterior mediastinal mass with draining sternal sinus tracts due to *Nocardia braziliensis*. West J Med 1997 July; 167:46-48)

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Figure 1. Multiple cutaneous sinus tracts discharging purulent material through the skin on the anterior chest wall.

Figure 2. Chest CT scan with intravenous contrast showing the anterior mediastinal mass with extension to the chest wall and right pectoral muscle.

sible for the decomposition of plant material. These organisms are occasionally pathogenic for humans and enter the body via inhalation or cutaneous inoculation. Asteroides complex (*N. farcinica*, *N. nova*, and *N. asteroides sensu strictu*) are responsible for most of the reported disease in the US and tend to infect people most commonly via the pulmonary route.[2] *Nocardia asteroides* organisms also have a predilection for hosts who are deficient in cell-mediated immunity. *N. braziliensis*, on the other hand, usually infects normal people primarily via the traumatized cutaneous route, and mainly infects rural workers in tropical and subtropic climates.[2] Cutaneous disease can usually be classified into four clinical types: mycetomas, lymphocutaneous or "sporotrichoid" infections, superficial skin infections (abscesses or cellulitis), and secondary involvement of disseminated infections.[3]

Mycetomas are chronic, indolent, and progressive infections caused by fungi (eumycetoma) or actinomycetes (actinomycetoma).[2,4,5] The incidence of each organism varies in different parts of the world.[5] In Mexico, *N. braziliensis* accounts for 86% of all mycetomas.[6] In Central and South America and India, *N. braziliensis* is also common, but some fungi, such as *Madurella grisea*, are equally prevalent.[4] This disease is uncommon in the United States and generally occurs in the southern states, near the Mexican border.[7] Mycetomas occur in areas subject to minor trauma and soil contamination, particularly the feet, but also the legs and hands.[4] The head, neck, and back have been involved predominantly in workers who carry contaminated objects on their backs or on their heads.[2,4] Characteristics of mycetomas include a tumorlike appearance, subcutaneous granulomata, and abscesses that drain via multiple cutaneous sinus tracts. Often, macroscopically visible granules drain from these tracts.[4] The triad of tumefaction, draining sinuses, and macro- or microscopic granules is usually present.[4,5] Our patient's lesions did not reveal granules upon needle aspiration. This likely represents either a sampling error or an earlier stage of the disease, since the rest of his clinical picture is most consistent with this category of primary nocardial skin disease.

Pathogenesis of mycetoma involves initial cutaneous trauma and inoculation, such as a puncture wound or abrasion from thorns, splinters, or animal scratches.[2–4] Weeks to months later, a small painless subcutaneous nodule appears at the injury site which spontaneously drains via sinus tracts to the skin. The infection then burrows deeper, suppurates, and forms more sinus tracts which drain superficially.[2,4] Drainage can be of a varying nature: serous, serosanguinous, or purulent with multiple granules that have distinguishing colors and characteristics depending on the organism involved.[4] These granules are clusters of organisms surrounded by inflammatory cells.[2] The cycle of invasion, suppuration, and drainage is continuous and indolent, and leads to massive local disfiguration and destruction.[2,5] Invasion of bone, muscle, and fascia is common. Since mycetomas occur mainly in developing nations among rural inhabitants, many people do not seek attention for years and develop impressive lesions. These lesions are seldom painful and systemic symptoms or dissemination are rare. Our patient routinely carried crates of fruit while shirtless. He probably sustained a cutaneous scratch or abrasion to his anterior chest wall by a crate which was contaminated with soil and *N. braziliensis*.

Therapy depends on the organism. Fungi are usually refractory to medical therapy and require surgical intervention along with antifungal medication. In contrast, actinomycete infections often respond to medical therapy alone, even with extensive bony and deep structure involvement.[8] Trimethoprim/sulfamethoxazole, sulfadiazine, and dapsone, with or without streptomycin, for an average duration of 9 months (4–18 months) have all been effective in producing an 85% cure or significant improvement.[4,8]

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* * *

Waking

Waking to odor so primal
it has no name but *me*.
To blankets, they say weight.
Nose and cheeks say cold. Warm
vibrating hip says curled cat,
asleep. A gradient of light
slits drape from sash,
says house, bridge,
fountain, gate. Says weather.
Says time. Suddenly, the ticking,
and every sound has name—
thump, hiss, clatter, squeak—
distinct from body.
Sense by sense, body comes to
the parsing, and I,
the nomenclator, wake.

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Editorial

The Alphabet Soup of Viral Hepatitis: Is G a New Flavi(or) in the Mix?

VIRAL HEPATITIS in humans has a long past but a short history. Illnesses resembling those produced by hepatitis A and B infections were described in antiquity; clearer references are found in the medical literature of the past two hundred years. Landmark epidemiological and transmission studies, showing beyond doubt the existence of at least two forms ("infectious" and "serum") of hepatitis, were not carried out until the middle of this century.[1] Even then, simple, reliable tests suitable for screening and follow-up of patients at risk did not become available until 1965, when Blumberg, Alter, and Visnich published their seminal—albeit serendipitous—observations of a new antigen.[2] They identified the serum as a novel antigen in an Australian aborigine, in the context of a study focused not on hepatitis, but on genetic polymorphisms of components of human serum. Indeed, Blumberg at first did not believe he had identified a new viral antigen. He later (wisely) modified his views and was awarded the Nobel Prize for Physiology and Medicine for discovering what we now call hepatitis B surface antigen.

Identification of the viral cause of infectious hepatitis, the hepatitis A virus (HAV), followed a few years later, and highly sensitive and specific tests for antibodies to both HAV and HBV are now widely available. Use of these tests in patients with acute or chronic hepatitis showed that there must be at least one other viral cause of hepatitis. In the late 1970s and 1980s, evidence for several candidate "viruses" was presented, but confirmation proved elusive.

It was not until 1989 that the hepatitis C virus was identified, leading to an explosion of new knowledge about this flavivirus that produces relatively mild acute hepatitis (only about one patient in three develops jaundice) but usually leads to chronic infection (~85% of those infected), with evidence of chronic hepatitis (~70–80% of those infected).

The delta agent (HDV) and the hepatitis E virus (HEV) were also described during the past 20 years, and their roles in liver disease have been defined (Table 1). Fortunately, infections with these agents are now relatively rare in the US. HAV, HBV, HCV, HDV, HEV, and other known viruses (such as cytomegalovirus, coxsackie virus, Epstein-Barr virus, and herpes simplex virus [HSV]) clearly are responsible for a substantial majority of acute and chronic hepatitis everywhere in the world. The viruses capable of causing chronic hepatitis and cirrhosis (HBV, HCV, HDV) are the major etiological agents for hepatocellular carcinoma as well.

Even though hepatitis viruses A–E have been identified, it is clear that at least one other viral cause of hepatitis must exist, because patients continue to have clinical illnesses (posttransfusion hepatitis; fulminant hepatic failure; cryptogenic hepatitis and cirrhosis; aplastic anemia following acute hepatitis) that seem to be due to viruses, yet have no evidence for infection with HAV, HBV, HCV, HDV, or HEV.

In this issue of THE WESTERN JOURNAL OF MEDICINE, Cheung, Keeffe, and Greenberg provide a summary of information regarding the "newest kid on the block," hepatitis G or GBV-C.[3*] As summarized in their paper and in Table 1 on the next page, HGV, like HCV, is a positive-stranded RNA virus of the flaviviridae family, independently isolated, cloned, sequenced, and characterized by investigators at Abbott Laboratories and Genelabs. HGV certainly is associated with hepatitis, and many of those infected with the virus become chronic carriers.

However, as also summarized by Cheung et al., there is scant evidence that HGV is an important player causing serious forms of acute hepatitis, and there is no evidence at all that it causes chronic hepatitis, cirrhosis, or hepatocellular carcinoma. Furthermore, chronic infection with this remarkably ubiquitous virus does not appear to affect the course, severity, or outcome of liver disease due to other causes (such as HBV or HCV), although data are few from patients with diverse causes of disease (alcohol, autoimmune causes, metabolic causes). The most striking association to cause concern is that between HGV and aplastic anemia following acute hepatitis.[4–6] Indeed, HGV was first identified and isolated from a patient with aplastic anemia.[4] The two other cases of aplastic anemia and HGV infection described thus far were both in young men who developed severe acute hepatitis followed in 3–5 weeks by pancytopenia.[5,6] Both were found to be HGV RNA–positive by polymerase chain reaction early in their illnesses, before receiving any blood products, and both were negative for HAV, HBV, HCV, EBV, and CMV. One was tested, and found negative, for infection with HEV, coxiella, and leptospira; the other had only IgG antibodies to parvovirus B19, indicating remote infection. Neither had evidence for autoimmune disease or other known causes of hepatitis. Neither patient had serum available from before the onset of illness—unfortunate, but not surprising—and we cannot be sure whether they were already carriers of HGV and developed acute hepatitis from another cause. This is a possibility in view of the high prevalence of HGV RNA–positive people in the general population (1–10%) (see Table 1 of Cheung et al., page 26[3]).

In a careful report that appeared too recently to be included in the review of Cheung et al., the role of HGV in transfusion-associated hepatitis was described.[7] Seventy-nine of 357 recipients of transfusions (22%) at the National Institutes of Health between 1972 and 1995

*See also the Review by Ramsey C. Cheung et al, "Hepatitis G Virus: Is it a Hepatitis Virus?," on pages 23–33 of this issue.

Table 1.—*Summary of Known Major Human Hepatitis Viruses*

Name	Genomic nucleic acid	Size of genome (kb)	Viral family	Major routes of transmission	Cause of chronic hepatitis or cirrhosis	Comments
A	RNA	7.5	Picorna	Fecal-oral	No	Rarely causes fulminant hepatitis
B	DNA	3.2	Hepadna	Parenteral; sexual	Yes (5–10%)	Rarely causes fulminant hepatitis
C	RNA	9.4	Flaviviridae	Parenteral	Yes (70–80%)	Major indication for liver transplantation in the US
D	RNA	1.7	Unclassified	Parenteral	Yes	Requires co-infection with HBV
E	RNA	7.5	Calici- or alpha-like	Fecal-oral	No	Mainly Third World countries; high fatality rate in pregnant women
G	RNA	9.1	Flaviviridae	Parenteral	Unknown	Role in causing liver disease unclear

developed hepatitis. Sixty-three of the 79 (80%) had acute HCV infection, and three had pre-existing HCV. Ten (13%) were infected with unidentified agents, and only three (4%) developed acute HGV infection alone with hepatitis. All three developed mild, anicteric hepatitis with mean peak serum alanine aminotransferase (ALT) 198 U/l, and there was poor correlation between levels of ALT and HGV RNA. Evidence for acute HGV infection occurred with similar frequency in patients who developed acute hepatitis C (5/53), those with minor elevations in ALT (so slight that they did not fulfill criteria for acute hepatitis) (12/100), and those with no evidence of posttransfusion hepatitis whatsoever (14/181) (P = 0.26). (In contrast, out of 157 controls, HGV infection developed in only one patient who was also hospitalized but did not receive transfusions.) Thus, 89% of all acute HGV infections were associated with no or minimal evidence of hepatitis. The authors concluded that "no causal relation between HGV and hepatitis has been established." These results throw additional doubt on the notion that HGV is the cause of aplastic anemia. Perhaps both the severe hepatitis and the anemia that occasionally occur in patients transfused with HGV-positive and HAV-, HBV-, HCV-negative blood are due to another, still uncharacterized, virus or viruses.

HGV clearly is a new flavivirus that infects humans, often chronically, and is associated with acute and chronic hepatitis. The type and severity of hepatitis that it causes (if it does so at all) is so minor as to cast doubt on the appropriateness of its being classified as a hepatitis virus at all. It may have a role in development of aplastic anemia, but in that regard, too, Koch's postulates remain unmet. Current evidence does not support a need to screen all blood products for HGV—a good thing, since no practical screening assay exists. The search for other viral causes of acute and chronic hepatitis, fulminant hepatic failure, cryptogenic cirrhosis, and aplastic anemia must continue. HGV is not the culprit.

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Onychomycosis—A Different Perspective

To the Editor: The article entitled, "Onychomycosis, New Therapies for an Old Disease" which appeared in the December 1996 issue of WJM[1] fails to discuss a number of important issues relevant to treating toenail onychomycosis with the new antifungal agents.

First of all, cost. The wholesale cost of twelve weeks of terbinafine 200 mg daily is about $500. The wholesale cost of three weekly pulses of itraconazole 400 mg daily is about $450. These are wholesale prices. Add the cost of the office visits to monitor the patient while taking the antifungal, plus the cost of a fungal culture, and the total cost to the patient will be close to $1,000. If the treating physician decides to get baseline and monitoring blood studies, these costs will push the total bill even higher.

Second, the reported cure rates ranging from 40 to 70% cited by the authors refer to treatment of toenails infected with dermatophyte fungi. Yeasts and other nondermatophyte fungal organisms cause a significant percentage of cases of onychomycosis. These nondermatophyte organisms do not respond as well to antifungal agents as do the dermatophytes. Consequently, identification of fungi should be mandatory and not done "whenever possible" as recommended by the authors. Another reason microscopy and fungal culture are mandatory is that not all dystrophic toenails are due to an infectious process. Psoriasis, chronic trauma, and injuries may produce dystrophic nails clinically indistinguishable from onychomycosis.

The frequency of relapse after successful treatment with itraconazole or terbinafine is unknown. The authors quote a range of 10 to 20% relapses after 1 year for itraconazole and terbinafine, and state this is far better than what occurs after treatment with griseofulvin. This data does not stand up to careful scrutiny. The numbers are too small, and the follow-up period of 1 year is too short to be meaningful. I am old enough to recall our enthusiasm when griseofulvin became available in the later 1950s. We found that we could frequently clear chronic fungal infections of the skin or nails, but that sooner or later most patients relapsed. It is too soon to establish the relapse rate for itraconazole and terbinafine.

Not mentioned in this paper is the intense promotional campaign on the part of Janssen Pharmaceuticals, the makers of itraconazole. Not only are there numerous advertisements in medical journals, ordinary magazines also have been peppered with advertisements urging patients to "kick the fungus" with itraconazole. Janssen has paid speakers to discuss antifungal therapy at hospitals and medical meetings, and I believe some of the authors of the article in The Western Journal of Medicine have received honoraria from Janssen Pharmaceuticals.

Is systemic treatment for toenail onychomycosis indicated? Successful clearing of toenail dermatophyte infections occurs in only 40 to 70% of patients; the relapse rate is unknown. For most patients, onychomycosis is a cosmetic nuisance which can be lessened by cutting, filing, or otherwise abrading the dystrophic nail. Sometimes onychomycosis results in grossly thickened nails which cause discomfort by contact with shoes. Vigorous mechanical thinning of the nail with a file or a small hand-held motorized abrading tool will usually provide comfort. Significant side effects for both of the new antifungals have been documented; admittedly they are infrequent. Does the benefit-to-risk ratio justify the use of these agents in onychomycosis of the toenails?

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* * *

Drs Gupta, Scher, De Doncker, Sauder, and Shear Respond

To the Editor: The authors thank Dr Epstein for his thoughtful and incisive comments regarding our article in the December 1996 issue of WJM which consisted principally of two case reports and was never intended to be a comprehensive overview of the management of onychomycosis.

With regard to the cost of treating toenail fungal infection, the newer antifungal agents are definitely less expensive overall than griseofulvin. Several pharmacoeconomic studies have concluded that it is not cost-effective to use griseofulvin over terbinafine, itraconazole, or fluconazole when treating onychomycosis of the toenails.[1–5] In a recent pharmacoeconomic survey, the total cost of regimen (including drug acquisition cost, medical management cost, and adverse drug effects management cost) when treating dermatophyte onychomycosis of the toenails was griseofulvin ($1981.9, 1997 US$), itraconazole (pulse therapy) ($716.8), itraconazole (continuous) ($1173.9), terbinafine ($783.4), and fluconazole ($1165.1, assuming a dose of 300 mg once a week for 9 months with a 300-mg tablet costing twice the current price of the 150-mg tablet).[5]

The authors agree that is is essential to confirm the diagnosis before starting therapy. Unfortunately, this is not consistently done by all health care providers.

For both itraconazole and terbinafine, the rate of recurrence of onychomycosis after successful treatment is approximately 10 to 15% 1 year after starting therapy[6,7] and less than 20% 2 years after start of treatment

(personal communication, Tosti A, March 1997). One should be careful to distinguish relapse from reinfection when discussing recurrence of disease. Recurrence of onychomycosis beyond a certain time point after stopping antifungal therapy (e.g., 1 1/2 years) is more likely to be caused by reinfection. Thus, it is important to educate the patient to take measures that will reduce reinfection with onychomycosis.

The authors are investigators and consultants to Pfizer, Janssen, and Novartis and as such often are asked to lecture for these companies. A conflict of interest declaration was submitted with our article. One of the authors (PDD) is employed by Janssen, as is published in the article.

In the majority of cases, onychomycosis is treated for noncosmetic reasons. In a sizeable proportion of patients this disease is associated with discomfort, pain, difficulty in wearing appropriate footwear and in walking, and the inability to perform activities of daily living to the maximum potential.[8] Onychomycosis, especially fingernail disease, can have an important impact on psychological well-being. Both family members and strangers may avoid contact with an individual with abnormal-looking nails for fear of becoming infected themselves. Fingernail onychomycosis in particular can interfere with the ability to perform certain tasks such as typing and playing musical instruments. Tinca pedis is often associated with onychomycosis and these may predispose to cellulitis, thrombophlebitis, urticaria, and hypersensitivity symptoms due to *Trichophyton* allergens and molds. In individuals with a sufficiently depressed immune system, systemic dissemination of fungal infection can take place.[6]

In regard to the benefit-risk ratio of the newer antifungal agents, with careful patient selection and counseling, data show that itraconazole, terbinafine, and fluconazole have a high benefit-to-risk ratio in the treatment of onychomycosis.[9]

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CORRECTION

In Dr Julie Madorsky's article in the June 1997 issue,[1] there is an editing error that changed the meaning of one of the author's points. In the editing process, in paragraph 2, the word "might" was inserted in the sentence, "... many of Dr Jack Kevorkian's assisted suicide cases [might] have had disabilities?" The corrected sentence should read as follows: "Might there be a connection between the beliefs about the perceived invalidity of persons with disabilities and the fact that, in addition to individuals with terminal illnesses, many of Dr Jack Kevorkian's assisted suicide patients had disabilities?"

"It is a fact," writes Dr Madorsky, "that several of Dr Kevorkian's clients were individuals who did not have a terminal disease, but who had physical disabilities such as multiple sclerosis. That was the point of my Commentary. It is one thing to assist the process of death in a person who has a terminal illness that is going to result in death within six months or less. It is an entirely different matter to cause death in a person who does not have a terminal condition, but a disabling condition."

The Editors

REFERENCE

1. Madorsky JG. Is the slippery slope steeper for people with disabilities? West J Med 1997 June; 166:410–411

CORRECTION

In Dr Arthur Rivin's article in the June 1997 issue,[1] there is an editing error in the two bulleted items on page 393. They should read as follows:

- A family conference with the entire ethics committee is cumbersome and sometimes intimidating; a smaller group of ethics committee members should represent the committee. Communication skills in those circumstances need to be taught.
- Care providers other than the attending physician need to have access to the bioethics committee.

The Editors

REFERENCE

1. Rivin AU. Futile care policy: lessons learned from three years' experience in a community hospital. West J Med 1997 June; 166:389-393

Lessons From the Practice

The Final Act

CHRIS DERK, MD, *MacDill Air Force Base, Florida*

It's 10:30 again. I look at the clock. I can't remember how the hours went by. I look in the eyes of the two women in front of me. They are the same eyes I saw not so long ago. The eyes of despair, pain, and fear, but yet with a small glimpse of hope.

When Mr. Walter, an 88-year-old gentleman with multi-infarct dementia, came to the emergency room, he didn't have long to live. He was clutching for breath and asking for help. The new murmur in Mr. Walter's chest was confirmed by echocardiography, and his only hope was emergent surgery. Consultants were scrambling to get their ideas on paper, and Mr. Walter's physician asked me to ascertain the family's wishes. That is when I first heard the question, "Is he DNR?" As one after the other medical staff learned about Mr. Walter, the same question was thrown at me. They were like actors who hadn't been told the Final Act. They had no scenario to go by. The question became more and more intense and more and more frequent. The burden I felt was very heavy, but it was my job. I was the senior resident. I was the one responsible to produce an answer for them. I had to get them the Final Act they were looking for.

I moved toward the two women in the waiting room and pulled a chair next to them. The three of us formed a circle as if we were going to share a secret. I looked in their eyes and tried to be as objective as possible, and still empathize with their feelings. They had just buried their mother, and now they only had each other to share their grief. But here I was, a stranger to them, telling them that it was time for their father to die.

"He needs a valve replacement. Without it, he will die."

The two sisters looked at each other.

"What do you think?" said one to the other.

"Would he have wanted it, or not?"

"Will he make it out of surgery?"

"What do you think, Doctor?"

They hadn't had time to mourn their mother and had no time to realize what was happening to their father, yet I was asking them to give me a rational answer to my question in the next few minutes, or hours. They were to give me a Final Act to a "play" called life that took so many years of living to complete.

After talking to all of the consultants, and after getting all of the statistics and possible scenarios, the two sisters approached me with tears in their eyes. They were giving me the Final Act.

"Let him go, but don't let him suffer, make him comfortable."

Is it ethical to put the family under such pressure in such a short time? Is it ethical that Mr. Walter didn't have a living will? Shouldn't Mr. Walter have written the Final Act? What is the role of his doctor in all of this; the role of his daughters? These are all questions that have been answered multiple times and in multiple ways, yet they recur and they still don't have a definitive answer.

There is a need to educate patients about what a living will means, and try to show them the responsibility and uncertainty that they leave behind for their loved ones to bear, when they don't have one. Death is a taboo subject but it needs to be publicized more, not only to doctors but also to patients. Death needs to become a more dignified end.

(Derk C. The final act. West J Med 1997 July; 167:54)

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2. Parkin DM, Clayton D, Black RJ, Masuyer E, Friedl HP, Ivanov E, et al. Childhood leukaemia in Europe after Chernobyl: 5 year follow-up. Br J Cancer 1996; 73:1006–1012

No author given:

3. Cancer in South Africa [editorial]. S Afr Med J 1994; 84(12):15

Books

4. Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996 [author of book is same as author of chapter]

5. Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995, pp 465–478 [authors of book differ from chapter author]

Correspondence

6. Shusterman D. Espresso maker's wrist [correspondence]. West J Med 1990; 152:721–722

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8. Field MJ, Tranquada RE, Feasley JC, editors. Health services research: work force and educational issues. Washington DC: National Academy Press; 1995. Contract No.: AHCPR282942008. Sponsored by the Agency for Health Care Policy and Research

9. Centers for Disease Control and Prevention. Recommendations and Reports: 1997 Revised guidelines for performing CD4+ T-cell determinations in persons infected with human immunodeficiency virus (HIV) MMWR 1997; 46(Jan 10):RR-2

Proceedings

10. Kimura J, Shibasaki H, editors. Recent advances in clinical neurophysiology. Proceedings of the 10th International Congress of EMG and Clinical Neurophysiology; 1995 Oct 15–19; Kyoto, Japan. Amsterdam: Elsevier; 1996

Mass Circulation Publications

11. Lee G. Hospitalizations tied to ozone pollution: study estimates 50,000 admissions annually. The Washington Post 1996 Jun 21; Sect A:3 (col 5)

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12. Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

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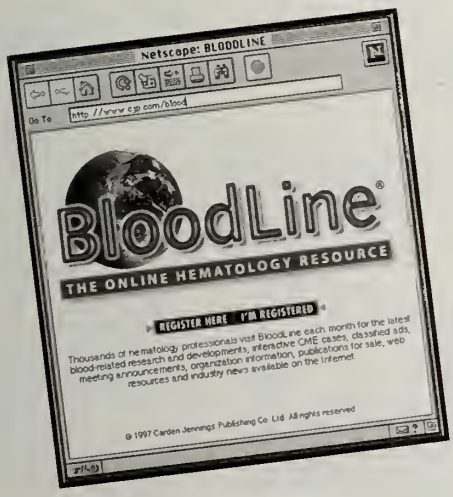

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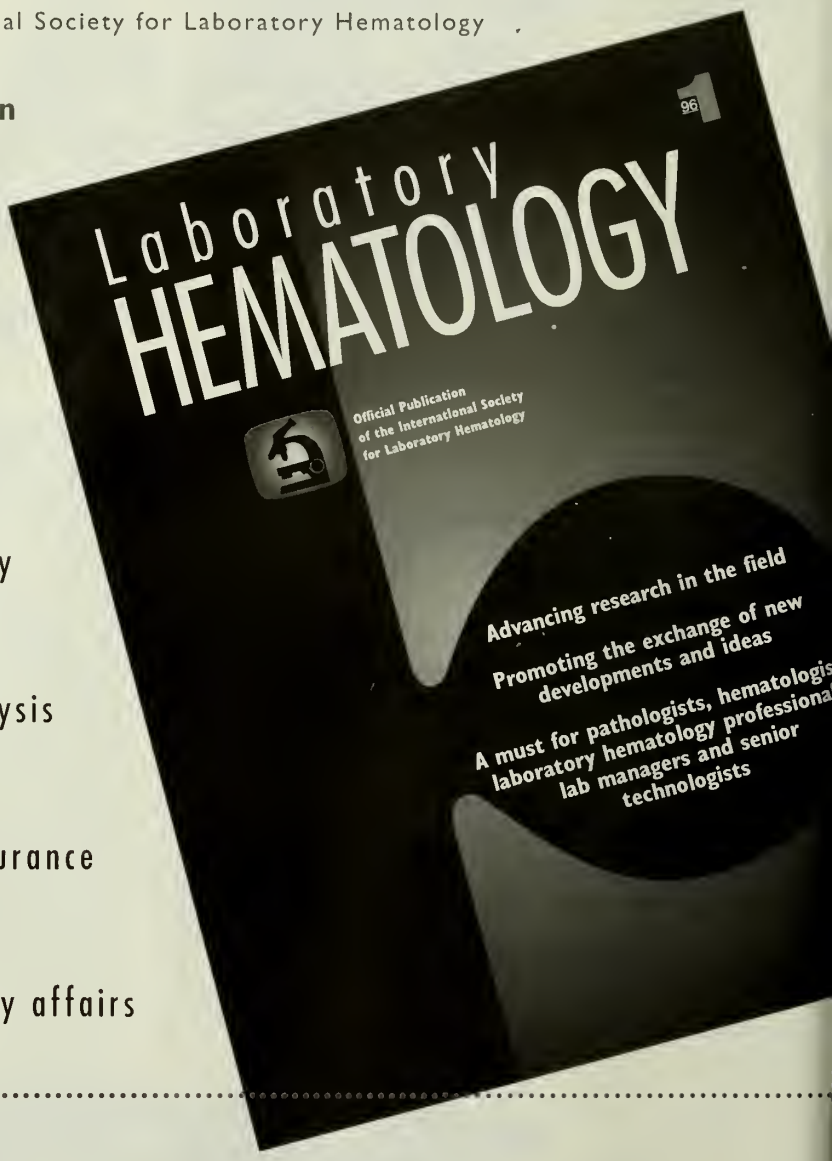

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Editorials, Lessons From The Practice . . .

Advertising Index

CARDEN JENNINGS PUBLISHING CO.
American Society of Blood & Marrow Transplantation 63
Bloodline 61
Cases in Cardiology . . . . . 4th Cover
Laboratory Hematology 62

SOUTHERN MEDICAL ASSOCIATION . . . . . 2nd Cover

THE WESTERN JOURNAL OF MEDICINE
WJM Subscription Order Form 2
WJM Special Issues Catalog . . . . . 3rd Cover

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The Western Journal of Medicine

VOLUME 167 • NUMBER 2

AUGUST 1997

ARTICLES

74 Violence Against Surgical Residents
C BARLOW and A RIZZO

79 Topical Lidocaine Adrenaline Tetracaine (LAT Gel) Versus Injectable Buffered Lidocaine for Local Anesthesia in Laceration Repair
A ERNST, E MARVEZ–VALLS, T NICK, T MILLS, L MINVIELLE; and D HOURY

82 Pathophysiology of the Thalassemias—The Albion Walter Hewlett Award Presentation
S SCHRIER

CONFERENCES AND REVIEWS

90 The Pelvic Floor in Health and Disease
A SHELTON and M WELTON

EPITOMES

99 Important Advances in Plastic Surgery

ALERTS, NOTICES, AND CASE REPORTS

103 Development of Hepatocellular Carcinoma After Clearance of Hepatitis C Virus With Interferon Therapy
M TONG, L LAI, and K MURAKAMI-MORI

106 Betaxolol and Drug–Induced Lupus Complicated by Pericarditis and Large Pericardial Effusion
J HARDEE, C ROLDAN, and T DU CLOS

109 Magnetic Resonance Imaging for the Diagnosis of Occult Pelvic Fractures: Two Case Reports
E MILLER, R DERLET, and M ANDERSON

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POEM

114 Physical
J DONOGHUE

LESSONS FROM THE PRACTICE

115 Serendipity
J NEELY

OTHER FEATURES

66 Subscription Information

69 Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming

117 Classified Advertising

124 Instructions for Authors

Detailed Table of Contents: 67, 68

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WJM10

The Western Journal of Medicine

VOLUME 167 • NUMBER 2 • AUGUST 1997

CONTENTS

BOSTON, MA
SEP 10 1997

ARTICLES

74 **Violence Against Surgical Residents**

CASSIE B. BARLOW, PhD, and ANNE G. RIZZO, MD

From the Armstrong Laboratory, Logistics Research Division, Wright Patterson AFB, Ohio; and Mike O'Callahan Federal Hospital, 99th Medical Group, Nellis AFB, Nevada.

79 **Topical Lidocaine Adrenaline Tetracaine (LAT Gel) Versus Injectable Buffered Lidocaine for Local Anesthesia in Laceration Repair**

AMY A. ERNST, MD, FACEP; EDUARDO MARVEZ-VALLS, MD, FACEP; TODD G. NICK, PHD; TREVOR MILLS, MD; LUCIA MINVIELLE, NP; and DEBRA HOURY

From the Department of Emergency Medicine, Vanderbilt University; Section of Emergency Medicine, Louisiana State University; University of Mississippi; and Tulane University School of Medicine.

82 **Pathophysiology of the Thalassemias—The Albion Walter Hewlett Award Presentation**

STANLEY L. SCHRIER, MD

From the Division of Hematology, Stanford University Medical School, Stanford, California.

CONFERENCES AND REVIEWS

90 **The Pelvic Floor in Health and Disease**

ANDREW A. SHELTON, MD, and MARK L. WELTON, MD

From the Department of Surgery, University of California San Francisco School of Medicine, San Francisco, California.

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Plastic Surgery

Items of progress in plastic surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance.

99 **Advances in Microvascular Free Tissue Transfer**

ASHTON A. KAIDI, MD, and ROBERT A. HARDESTY, MD, FACS

100 **Facial Fractures in Children**

DANIEL B. KIM, MD; MANUEL SACAPANO; and ROBERT A. HARDESTY, MD, FACS

100 **Computerized CO_2 Laser Resurfacing for Aesthetic Management**

STEVEN M. HOEFFLIN, MD, FACS

101 **Correction of Velopharyngeal Insufficiency Using the Furlow Double-Opposing Z-plasty**

LINDA L. D'ANTONIO, PHD

ALERTS, NOTICES, AND CASE REPORTS

103 **Development of Hepatocellular Carcinoma After Clearance of Hepatitis C Virus With Interferon Therapy**

MYRON J. TONG, PHD, MD; LILLIAN P. LAI, BS; and KAORU MURAKAMI-MORI, PHD, MD

From the Liver Center and Institute of Molecular Medicine, Huntington Memorial Hospital, Pasadena, California.

106 **Betaxolol and Drug-Induced Lupus Complicated by Pericarditis and Large Pericardial Effusion**

JAMES T. HARDEE, MD; CARLOS A. ROLDAN, MD; and TERRY W. DU CLOS, MD, PHD

From the Department of Internal Medicine , University of New Mexico School of Medicine, and the Divisions of Cardiology and Rheumatology, Veterans Affairs Medical Center, Albuquerque, New Mexico.

109 **Magnetic Resonance Imaging for the Diagnosis of Occult Pelvic Fractures: Two Case Reports**

ERIK C. MILLER, MD; ROBERT W. DERLET, MD; and MARK ANDERSON, MD

From the Division of Emergency Medicine and the Department of Radiology, University of California Davis Medical Center, Sacramento, California.

POEM

114 **Physical**

JOHN DONOGHUE

LESSONS FROM THE PRACTICE

115 **Serendipity**

JAMES C. NEELY, MD

OTHER FEATURES

66 WJM Subscription Information

69 Continuing Medical Education Activities

117 Classified Advertising

124 Instructions for Authors

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September 11–13—**Computer Training for Physicians.** UCSD at National University San Diego. Thurs.–Sat. 18 hrs. $575. Contact: OCME (619) 534-3940.

September 25–27—**Computer Training for Physicians.** UCSD at National University San Diego. Thurs.–Sat. 18 hrs. $575. Contact: OCME (619) 534-3940.

October 17–19—**Computer Training for Physicians.** UCSD at National University San Diego. Thurs.–Sat. 18 hrs. $575. Contact: OCME (619) 534-3940.

November 20–22—**Computer Training for Physicians.** UCSD at National University San Diego. Thurs.–Sat. 18 hrs. $575. Contact: OCME (619) 534-3940.

December 11–13—**Computer Training for Physicians.** UCSD at National University San Diego. Thurs.–Sat. 18 hrs. $575. Contact: OCME (619) 534-3940.

January 28–31, 1998—**Medicine Meets Virtual Reality: Art, Science, Healthcare Evolution.** UCSD at San Diego Hyatt Regency. Wed.–Sat. Contact: Karen Morgan (760) 751-8841.

DERMATOLOGY

September 27–28—**The Skin From A to Z.** UCSF at Laurel Heights Campus, UCSF. Sat.–Sun. 10 hrs. $275. Contact: UCSF.

EMERGENCY MEDICINE

August 19–20—**High Risk Emergency Medicine.** Sponsored by National ACEP & Emergency Physicians' Medical Group. Tues.–Wed. Mission Valley Hilton, San Diego. 15 hrs. $299-499. Contact: Nations Executive Travel (800) 651-CEME.

October 17–19—**Essentials in Emergency Medicine and Urgent Care.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency La Jolla, San Diego. Method, AV, L, SB, W. $495. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

October 20–24—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon.–Fri. 32 hrs. $495. Contact: OCME (619) 534-3940.

November 10–14—**Emergency Medicine Symposium II.** UCSD at La Jolla Marriott. Mon.–Fri. 32 hrs. $495. Contact: OCME (619) 534-3940.

December 15–19—**Emergency Medicine Symposium II.** UCSD at UCSD San Diego. Mon.–Fri. 32 hrs. $495. Contact: OCME (619) 534-3940.

FAMILY PRACTICE/PRIMARY CARE

August 18–22—**Essentials of Primary Care: A Core Curriculum for Practice in the Managed Care Era.** UCSF at Squaw Creek Resort, N. Lake Tahoe. Mon.–Fri. 25 hrs. $625. Contact: UCSF.

August 22–24—**Primary Care Medicine: A Practical Approach.** Scripps Clinic at Le Meridien San Diego at Coronado, San Diego. Fri.–Sun. 16 hrs. Contact: Laurel Steigerwald, Dept. Academic Affairs 403-C. Scripps Clinic, 10666 N. Torrey Pines Rd., La Jolla 92037. (619) 554-8556.

September 20—**Health for the 21st Century (Women's Health in 1997).** UCSD at Town and Country, San Diego. Sat. 5 hrs. Contact: Kurt Benirschke (619) 534-2618.

September 25–27—**HIV, AID & Women.** OCME at La Jolla Marriott, San Diego. Thurs.–Sat. 14 hrs. $175. Contact: OCME (619) 534-3940.

September 27–30—**OB/GYN Review.** USC at Red Lion Hotel, Glendale. Sun.–Tues. 38 hrs. Contact: USC.

September 27—**2nd Annual Women's Health Symposium.** UCD at Davis Medical Center, Sacramento. Sat. Contact: UCD.

October 2–4—**Primary Care Orthopaedics.** UCSD at Hyatt Regency, La Jolla. Thurs.–Sat. 15 hrs. $575. Contact: OCME (619) 534-3940.

November 20–22—**Women's Health Issues in Primary Care.** UCSD at Hyatt Regency, La Jolla. Thurs.–Sat. 18 hrs. $300. Contact: OCME (619) 534-3940.

GERIATRICS

September 4–6—**Sports Medicine for the Mature Athlete.** OCME at Sheraton Grande Torrey Pines, La Jolla. Thurs.–Sat. Contact: OCME (619) 534-3940.

November 10–12—**Geriatrics Update, 1997.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $475. Mon.–Wed. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

INFECTIOUS DISEASE

September 25–27—**HIV, AID & Women.** OCME at La Jolla Marriott, San Diego. Thurs.–Sat. 14 hrs. $175. Contact: OCME (619) 534-3940.

November 7–9—**Advances in Infectious Disease.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $475. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

INTERNAL MEDICINE

August 17–20—**New Advances in Internal Medicine.** UCD at Embassy Suites, Monterey. Sun.–Fri. Contact: UCD.

August 22–24—**Primary Care Medicine: A Practical Approach.** Scripps Clinic at Le Meridien San Diego at Coronado, San Diego. Fri.–Sun. 16 hrs. Contact: Laurel Steigerwald, Dept. Academic Affairs 403-C. Scripps Clinic, 10666 N. Torrey Pines Rd., La Jolla 92037. (619) 554-8556.

September 26–30—**Internal Medicine 1997—Fall Program.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $675. Fri.–Tues. 30 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

November 22—**Management of Dyspepsia, Peptic Ulcer Disease and Gastric Cancer.** Sat. 4 hrs. $20. Contact: OCME (619) 534-3940.

NEPHROLOGY

January 29–31, 1998—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at La Jolla Marriott. Thurs.–Sat. 17 hrs. $425.

NEUROLOGY

October 16–17—**Neuroradiology Update.** Thu.–Fri. Hotel Del Coronado, Coronado, California. $300. Sponsored by UC San Diego. Information: Ryals & Associates, Inc., PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773; Fax: (770) 552-9859; http://www.ryalsmeet.com.

October 20–22—**Neurology and Outpatient Psychiatry in Primary Care.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency La Jolla, San Diego. Method: AV, L, SB, W. $495. Mon.–Wed. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Education Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education, (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

October 25—**"Brain Attack!" '97.** UCLA Stroke Center at Beverly Hilton, Beverly Hills. Sat. 6.5 hrs. Contact: Office of CME (310) 794-2620.

NEUROSURGERY

September 13–17—**1996-1997 Temporal Bone Surgical Dissection Courses.** The House Ear Institute at Los Angeles. Sat.-Wed. 48 hrs. $1,300. Contact: House Ear Institute, 2100 W. Third St., Los Angeles 90057. (213) 483-4431, ext. 7079.

October 11–15—**1996-1997 Temporal Bone Surgical Dissection Courses.** The House Ear Institute at Los Angeles. Sat.-Wed. 48 hrs. $1,300. Contact: House Ear Institute, 2100 W. Third St., Los Angeles 90057. (213) 483-4431, ext. 7079.

November 1–5—**1996-1997 Temporal Bone Surgical Dissection Courses.** The House Ear Institute at Los Angeles. Sat.-Wed. 48 hrs. $1,300. Contact: House Ear Institute, 2100 W. Third St., Los Angeles 90057. (213) 483-4431, ext. 7079.

ONCOLOGY

September 13—**2nd Annual Cancer Research Program.** UCD at Sierra Health Foundation, Sacramento. Fri. 6 hrs. $95. Contact: UCD.

October 25—**Interventional Approach to Cancer Care.** St. Mary Medical Center at Holiday Inn Victorville. Sat. 8 hrs. $90. Contact: Yvonne Newton, CTR, St. Mary Regional Medical Center, 18300 Highway 18, Apple Valley, 92307 (760) 242-2311, ext. 6111.

January 16–17, 1998—**Radiotherapy to Reduce Restenosis.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri.–Sat. 16.5 hrs. Contact: Laurel Steigerwald, Scripps Clinic Dept. Academic Affairs 403c, 10666 N. Torrey Pines Road, La Jolla, 92037 (619) 554-8556.

OTOLARYNGOLOGY

September 13–17—**1996-1997 Temporal Bone Surgical Dissection Courses.** The House Ear Institute at Los Angeles. Sat.–Wed. 48 hrs. $1,300. Contact: House Ear Institute, 2100 W. Third St., Los Angeles 90057. (213) 483-4431, ext. 7079.

October 11–15—**1996–1997 Temporal Bone Surgical Dissection Course.** House Ear Institute at Los Angeles. Sat.–Wed. 48 hrs. $1,300. Contact: House Ear Institute (213) 483-4431.

November 1–5—**1996-1997 Temporal Bone Surgical Dissection Course.** House Ear Institute at Los Angeles. Sat.–Wed. 48 hrs. $1300. Contact: House Ear Institute, 2100 W. Third St., Los Angeles, CA 90057. (213) 483-4431, ext. 7079.

PEDIATRICS

September 18–21—**Practical Pediatrics.** American Academy of Pediatrics at Fairmont Hotel. San Francisco. Thurs.–Sun. 19 hrs. $495. Contact: AAP P.O. Box 77-2862, Chicago, IL 60678-2862 (800) 433-9016 ext. 6796 or 7657.

September 25–27—**The Fetus & Newborn: State-of-the-Art Care.** Contemporary Forums at Hotel del Coronado, San Diego. Thurs.–Sat. 16 hrs. $415. Contact: Contemporary Forums, 11900 Silvergate Drive, Dept. 348, Dublin, CA, 94568. (510) 828-7100, ext. 0.

October 25–28—**Pediatric Facial Plastic Surgery.** UCD at Monterey Plaza Hotel. Sat.–Tues. Contact: UCD.

January 24, 1998—**Update in Behavioral/Developmental Pediatrics.** UCSF at campus of UCSF. Sat. Contact: UCSF.

PSYCHIATRY

November 14–16—**43rd Annual Group Therapy Symposium.** UCSF at Mark Hopkins Hotel, San Francisco. Fri.–Sun. 20 hrs. $340. Contact: UCSF.

PSYCHOLOGY

October 18—**New Treatment Advances for Psychosis.** UCD at UC Davis Medical Center, Sacramento. Sat. Contact: UCD.

RADIOLOGY

August 31–September 4—**Neuroradiology Review; Including the Head, Neck and Spine.** Sun.–Thu. The Four Seasons Hotel, Newport Beach, California. $725. Sponsored by UC Irvine. Information: Ryals & Associates, Inc., PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773; Fax: (770) 552-9859; http://www.ryalsmeet.com.

September 20–21—**Ultrasound Update: 1997.** UCD at DoubleTree Hotel, Sacramento. Sat.–Sun. Contact: UCD.

October 14–18 & 21–25—**Nuclear Medicine Mini-Fellowship.** UCSD at UCSD Medical Center. Tues.–Sat. 44 hrs. $3,000. Contact: David Yeung (619) 534-6682.

October 16–17—**Neuroradiology Update.** Thu.–Fri. Hotel Del Coronado, Coronado, California. $300. Sponsored by UC San Diego. Information: Ryals & Associates, Inc., PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773; Fax: (770) 552-9859; http://www.ryalsmeet.com.

October 17–19—**17th Annual Comprehensive Review of Vascular & Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Fri.–Sun. 14.5 hrs. $325. Contact: Ryals & Assoc. (770) 641-9773.

October 20–24—**Multispecialty Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon.–Fri. Contact: Ryals & Assoc. (770) 641-9773.

October 20–24—**22nd Annual San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon.–Fri. Contact: Ryals & Assoc. (770) 641-9773.

October 22–26—**Musculoskeletal MR.** Wed.–Sun. The Westin Resort Hotel, Hilton Head, SC. $550. Sponsored by UC San Diego. Information: Ryals & Associates, Inc., PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773; Fax: (770) 552-9859; http://www.ryalsmeet.com.

January 16–17, 1998—**Radiotherapy to Reduce Restenosis.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri.–Sat. 16.5 hrs. Contact: Laurel Steigerwald, Scripps Clinic Dept. Academic Affairs 403c, 10666 N. Torrey Pines Road, La Jolla, 92037 (619) 554-8556.

SURGERY

September 5–7—**Surgery: Science Advancing the Art.** UC Irvine at La Quinta Desert Springs Resort (Palm Springs). Fri.–Sun. 7 hrs. $250. Contact: Medical Student Conference Committee c/o Medical Education. UC Irvine, School of Medicine, P.O. Box 4089, Irvine 92717-4089.

September 19–20—**3rd Annual Surgical Review: Update in Minimally Invasive Surgery, Trauma and Ultrasound.** UCD at David Grant Medical Center, Fairfield. Fri.–Sat. Contact: UCD.

October 4–5—**New Directions in Lasers & Cosmetic Surgical Procedures: A Hands-On Course.** UCD at UC Davis Medical Center, Sacramento. Sat.–Sun. Contact: UCD.

GENERAL/MULTIDISCIPLINARY

August 16–17—**ACLS Provider.** AHA at San Leandro. Sat.–Sun. 16 hrs. $170. Contact: CPR Seminars (510) 632-6135.

August 26—**ACLS Instructor Renewal.** AHA at Concord. Tues. $100. Contact: Rozann (510) 754-7900 or Alice (510) 828-1563.

September 4—**ACLS Renewal.** AHA at Fremont. 6 hrs. Thurs. $100. Contact: Rozann (510) 754-7900 or Alice (510) 828-1563.

September 15–18—**Orientation Course in Hyperbaric Medicine.** Long Beach Memorial Medical Center. Mon.–Thurs. 27.5 hrs. $550. Contact: Celia Loney or Don Winant (562) 933-6951.

September 18–21—**8th Annual Conference of The American Academy of Pain Management.** Alexis Park Hotel & Spa, Las Vegas, Nevada. Contact: AAPM, (209) 533-9744; Email: aapm@aapainmanage.org; Website: www.aapainmanage.org.

September 19—**Student Health Connect.** UCSD. Fri. 8.5 hrs. $50. Contact: Sherry Torok (619) 292-2092.

September 19—**Wound Care Symposium.** Long Beach Memorial Medical Center. Fri. 7.5 hrs. $100. Contact: Celia Loney or Don Winant (562) 933-6951.

September 29 & October 6—**ACLS Instructor Course.** AHA at Concord. 10 hrs. Mon. $195. Contact: Rozann (510) 754-7900 or Alice (510) 828-1563.

October 3—**Pre-ACLS Study Workshop.** AHA at San Leandro. Fri. 7.5 hrs. $50–$70. Contact: CPR Seminars (510) 632-6135.

October 11–12—**Cost Effective Evaluation of Functional Capacity.** UCSD at OrthoMed, La Jolla. Sat.–Sun. 14 hrs. $450. Contact: Kerri Kazala (619) 550-7008.

October 22–25—**Wound Management Workshop.** UCSD at La Jolla Marriott. Wed.–Fri. 17 hrs. $475. Contact: Edith Bookstein (619) 454-3212.

October 24—**ACLS Renewal.** AHA at San Francisco. Fri. 6 hrs. $100. Contact: CPR Seminars (510) 632-6135.

October 25–26—**ACLS Provider.** AHA at San Francisco. Fri. 16 hrs. $170. Contact: CPR Seminars (510) 632-6135.

October 23–26—**Nevada Academy of Family Physicians 9th Annual CME/Golf Meeting.** The Orleans Hotel & Casino, Las Vegas. 19 hrs. Contact: Barbara Bolling, NAFP, PO Box 27713, Las Vegas, NV 89126-1713. (702) 228-5822.

November 3–6—**Orientation Course in Hyperbaric Medicine.** Long Beach Memorial Medical Center. Mon.–Thurs. 27.5 hrs. $550. Contact: Celia Loney or Don Winant (562) 933-6951.

November 7—**Wound Care Symposium.** Long Beach Memorial Medical Center. Fri. 7.5 hrs. $100. Contact: Celia Loney or Don Winant (562) 933-6951.

January 28–31, 1998—**Medicine Meets Virtual Reality:6. Art, Science, Technology: Healthcare (R)Evolution.** San Diego Hyatt Regency. Wed.–Sat. Contact: AMA, Inc. (760) 741-8841.

February 13–16, 1998—**California Academy of Family Physicians 50th Annual Scientific Assembly.** Anaheim Hilton and Towers. $275–$385. 26+ hrs. Contact: Clark W. Franklin, California Academy of Family Physicians, 114 Sansome St., Suite 1305, San Francisco, CA 94104-3824. (415) 394-9121; fax (415) 394-9119; Email: cfranklin@familydocs.org.

HOME STUDY/SELF-ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

The listing of continuing medical education programs in Idaho is compiled by the Ada County Medical Society. To

list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701. (208) 336-2930.

Brochures, course information, and registration forms are available from the contact person or organization.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

August 16—**Update in Primary Care (NMHMA).** Saturday. Albuquerque. Contact: Kelly Little, (505) 828-0237.

September 12–13—**American College of Surgeons Scientific Program.** Albuquerque. Fri.-Sat. Contact: Kelly Little, (505) 828-0237.

September 22–26—**MMI Healthcare Risk Management Certificate Program (HRMCP).** Albuquerque Marriott Hotel. Mon.-Fri. Contact: Gail Harris, (505) 883-0266.

January 23–24, 1998—**28th Annual Winter Pediatric Orthopaedic Seminar.** Albuquerque. Fri.-Wed. Contact: UNM Continuing Medical Education, Campus Box 713, Albuquerque, NM 87131-5126. (505) 272-3942, fax (505) 272-8604.

Satellite Courses

Immunization Update 1997
September 17

Hepatitis C
Sometime in November

Contact: Joe Treat, Immunization Program, (505) 827-2366

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UANS:	Utah Association of Neurological Surgeons, 24 S 1100 East, Ste 302, Salt Lake City 84102. (801) 531-7806.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

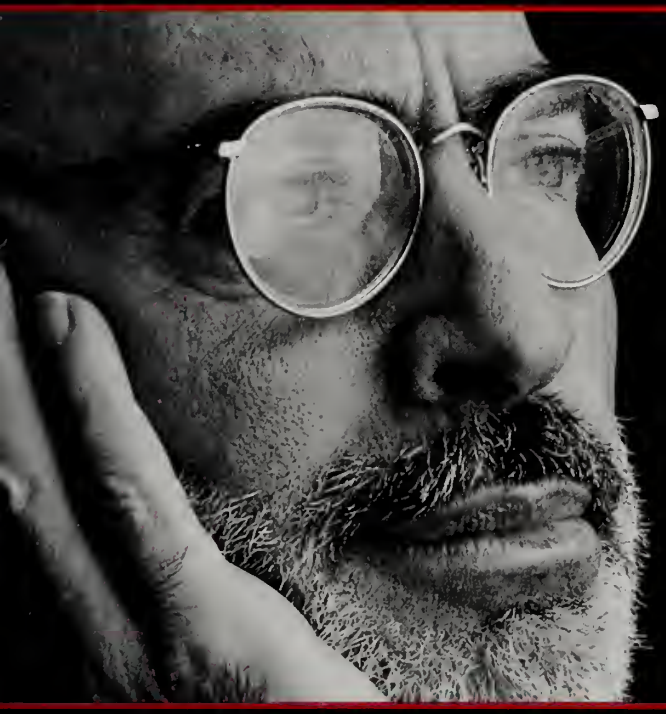
U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

In hypertension

HE KNOWS THE PROOF IS IN THE PERFORMANCE



THAT'S WHY HE PRESCRIBES ADALAT CC

Efficacy comparable to Procardia XL®[1,2] and Norvasc®*[3,4]

Similar safety profile† to Procardia XL[1,3] and Norvasc[3,4]

Substantially lower cost than Procardia XL and Norvasc‡[5]

Once-A-Day

Adalat® CC
nifedipine EXTENDED RELEASE TABLETS

30mg, 60mg & 90mg

A PRACTICAL CHOICE

Adalat CC is not indicated for angina. It should be taken on an empty stomach. As with all distinct pharmacologic entities, switching from one to another may necessitate careful titration and patient monitoring.

*Procardia XL (nifedipine) and Norvasc (amlodipine besylate) are registered trademarks of Pfizer Labs Division, Pfizer Inc.

†Frequency and type of side effects are typical of dihydropyridine calcium channel blockers.[6]

‡Calculations based on suggested Average Wholesale Price (AWP).[5] AWP is from a published price list and may or may not represent the actual price to pharmacists or consumers.

Please see brief summary of Prescribing Information on following page.

Once-A-Day

Adalat® CC nifedipine EXTENDED RELEASE TABLETS

30mg, 60mg & 90mg

A PRACTICAL CHOICE

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION
For Oral Use

PZ5DDD468S 9/96

INDICATION AND USAGE: ADALAT CC is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS: Known hypersensitivity to nifedipine

WARNINGS. Excessive Hypotension: Although in most patients the hypotensive effect of nifedipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients using concomitant beta-blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients who received immediate release capsules together with a beta-blocking agent and who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta-blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine-treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery.

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction upon starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.

Beta-Blocker Withdrawal: When discontinuing a beta-blocker it is important to taper its dose, if possible, rather than stopping abruptly before beginning nifedipine. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of nifedipine treatment will not prevent this occurrence and an occasion has been reported to increase it.

Congestive Heart Failure: Rarely, patients (usually while receiving a beta blocker) have developed heart failure after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to be of less benefit to these patients, owing to their fixed impedance to flow across the aortic valve.

PRECAUTIONS: General - Hypotension: Because nifedipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of ADALAT CC is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure (See WARNINGS).

Peripheral Edema: Mild to moderate peripheral edema occurs in a dose-dependent manner with ADALAT CC. The placebo subtracted rate is approximately 8% at 30 mg, 12% at 60 mg and 19% at 90 mg daily. This edema is a localized phenomenon, thought to be associated with vasodilation of dependent arterioles and small blood vessels and not due to left ventricular dysfunction or generalized fluid retention. With patients whose hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Information for Patients: ADALAT CC is an extended release tablet and should be swallowed whole and taken on an empty stomach. It should not be administered with food. Do not chew, divide or crush tablets.

Laboratory Tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms; however, cholestasis with or without jaundice has been reported. A small increase (<5%) in mean alkaline phosphatase was noted in patients treated with ADALAT CC. This was an isolated finding and it rarely resulted in values which fell outside the normal range. Rare instances of allergic hepatitis have been reported with nifedipine treatment. In controlled studies, ADALAT CC did not adversely affect serum uric acid, glucose, cholesterol or potassium.

Nifedipine, like other calcium channel blockers, decreases platelet aggregation *in vitro*. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some nifedipine patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

Positive direct Coombs' test with or without hemolytic anemia has been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Although nifedipine has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.

Drug Interactions: Beta-adrenergic blocking agents: (See WARNINGS).

ADALAT CC was well tolerated when administered in combination with a beta blocker in 187 hypertensive patients in a placebo-controlled clinical trial. However, there have been occasional literature reports suggesting that the combination of nifedipine and beta-adrenergic blocking drugs may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina in patients with cardiovascular disease.

Digitalis: Since there have been isolated reports of patients with elevated digoxin levels, and there is a possible interaction between digoxin and ADALAT CC, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing ADALAT CC to avoid possible over- or under-digitalization.

Coumarin Anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

Quinidine: There have been rare reports of an interaction between quinidine and nifedipine (with a decreased plasma level of quinidine).

Cimetidine: Both the peak plasma level of nifedipine and the AUC may increase in the presence of cimetidine. Ranitidine produces smaller non-significant increases. This effect of cimetidine may be mediated by its known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of nifedipine. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. In rodents, rabbits and monkeys, nifedipine has been shown to have a variety of embryotoxic, placentotoxic and fetotoxic effects, including stunted fetuses (rats, mice and rabbits), digital anomalies (rats and rabbits), rib deformities (mice), cleft palate (mice), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal deaths (rats, mice and rabbits), prolonged pregnancy (rats, not evaluated in other species), and decreased neonatal survival (rats, not evaluated in other species). On a mg/kg or mg/m^2 basis, some of the doses associated with these various effects are higher than the maximum recommended human dose and some are lower, but all are within an order of magnitude of it.

The digital anomalies seen in nifedipine-exposed rabbit pups are strikingly similar to those seen in pups exposed to phenytoin, and these are in turn similar to the phalangeal deformities that are the most common malformation seen in human children with *in utero* exposure to phenytoin.

There are no adequate and well-controlled studies in pregnant women. ADALAT CC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Nifedipine is excreted in human milk. Therefore, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE EXPERIENCES: The incidence of adverse events during treatment with ADALAT CC in doses up to 90 mg daily were derived from multi-center placebo-controlled clinical trials in 370 hypertensive patients. Atenolol 50 mg once daily was used concomitantly in 187 of the 370 patients on ADALAT CC and in 64 of the 126 patients on placebo. All adverse events reported during ADALAT CC therapy were tabulated independently of their causal relationship to medication.

The most common adverse event reported with ADALAT® CC was peripheral edema. This was dose related and the frequency was 18% on ADALAT CC 30 mg daily, 22% on ADALAT CC 60 mg daily and 29% on ADALAT CC 90 mg daily versus 10% on placebo.

Other common adverse events reported in the above placebo-controlled trials include: Headache (19%, versus 13% placebo incidence); Flushing/heat sensation (4%, versus 0% placebo incidence); Dizziness (4%, versus 2% placebo incidence); Fatigue/asthenia (4%, versus 4% placebo incidence); Nausea (2%, versus 1% placebo incidence); Constipation (1%, versus 0% placebo incidence).

Where the frequency of adverse events with ADALAT CC and placebo is similar, causal relationship cannot be established.

The following adverse events were reported with an incidence of 3% or less in daily doses up to 90 mg:

Body as a Whole/Systemic: chest pain, leg pain **Central Nervous System:** paresthesia, vertigo **Dermatologic:** rash **Gastrointestinal:** constipation **Musculoskeletal:** leg cramps **Respiratory:** epistaxis, rhinitis **Urogenital:** impotence, urinary frequency.

Other adverse events reported with an incidence of less than 1.0% were:

Body as a Whole/Systemic: cellulitis, chills, facial edema, neck pain, pelvic pain, pain **Cardiovascular:** atrial fibrillation, bradycardia, cardiac arrest, extrasystole, hypotension, palpitations, phlebitis, postural hypotension, tachycardia, cutaneous angiectases **Central Nervous System:** anxiety, confusion, decreased libido, depression, hypertonia, insomnia, somnolence **Dermatologic:** pruritus, sweating **Gastrointestinal:** abdominal pain, diarrhea, dry mouth, dyspepsia, esophagitis, flatulence, gastrointestinal hemorrhage, vomiting **Hematologic:** lymphadenopathy **Metabolic:** gout, weight loss **Musculoskeletal:** arthralgia, arthritis, myalgia **Respiratory:** dyspnea, increased cough, rales, pharyngitis **Special Senses:** abnormal vision, amblyopia, conjunctivitis, diplopia, tinnitus **Urogenital/Reproductive:** kidney calculus, nocturia, breast engorgement.

The following adverse events have been reported rarely in patients given nifedipine in other formulations: allergenic hepatitis, alopecia, anemia, arthritis with ANA (+), depression, erythromelalgia, exfoliative dermatitis, fever, gingival hyperplasia, gynecomastia, leukopenia, mood changes, muscle cramps, nervousness, paranoid syndrome, purpura, shakiness, sleep disturbances, syncope, taste perversion, thrombocytopenia, transient blindness at the peak plasma level, tremor and urticaria.

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UNIVERSITY OF NEBRASKA. October 6–8—**5th International Symposium "Blood Cell Transplantation."** Omaha. Mon.–Wed. $350. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. October 10—**5th Annual College of Medicine Alumni Day**. Omaha. Fri. Free. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. December 11–13—**Obstetrics & Gynecology Conference**. Bally's, Las Vegas, NV. Thu.-Sat. $325. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha NE 68198-5651. (800) 642-1095.

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Articles

Violence Against Surgical Residents

CASSIE B. BARLOW, PHD, *Wright Patterson AFB, Ohio; and* ANNE G. RIZZO, MD, *Nellis AFB, Nevada*

Violence against hospital personnel is underreported (less than one in five assaults), and accurate statistics as to the rate of violence against hospital personnel are thus difficult to establish. In the psychiatric discipline, an abundance of information has been published regarding violence in the health care setting, but few studies have examined violence outside psychiatric hospitals or by patients not diagnosed with psychiatric ailments. Using a survey that elicits information about workplace violence, we sought to gauge the prevalence of violent acts affecting general hospital workers who treat victims of violence on a daily basis. The survey was completed by a cohort of surgical staff nationwide (475 responses from 57 residency programs). Two hundred and eighty residents reported having witnessed one or more physical attacks, and 179 reported having been attacked. Violent acts were more likely to be committed in a public hospital than a private institution ($P = 0.05$). As shown in previous research, most attacks occurred in the emergency room ($P = 0.01$); the wards and parking lot were next in frequency. Women residents were more likely than men to call hospital security to intervene in a potentially violent situation ($P = 0.04$), and junior residents (postgraduate years 1–4) were more likely to be attacked than senior residents (≥5 years) ($P = 0.04$). The attacker was most likely to be a young black male between ages 19 and 30 ($P = 0.01$). We found no statistical relationship between the attacker and the victim regarding sex or race. Of the 475 respondents, 470 reported that they carry a gun themselves or know someone in the hospital environment who carries a gun.

(Barlow CB, Rizzo AG. Violence against surgical residents. West J Med 1997 August; 167:74–78)

Violence and conflict seem to be increasingly common aspects of everyday life. One million US inhabitants die each year as a result of intentional homicide or suicide; gunshot wounds are the leading cause of death in black and white teenage boys.[1] The National Institute for Occupational Safety and Health reports that violence "is a major contributor to occupational injury and death." Every week, 18,000 workers are assaulted at work, resulting in millions of lost workdays and millions of dollars in lost wages.[2] It has been suggested that the frequency and severity of work-related violence also are increasing, as are the numbers of different work groups involved,[3] which include police and prison officers, housing office staff, social workers, nurses, teachers, postal carriers, bar staff, retail sales staff, post office workers, and those involved in transport and banking. Violence seems to be most likely to occur where services are being provided—in a hospital, for example.

The majority of trauma patients in inner-city and university-based hospitals are victims of violence. Surgical residents and staff regularly deal with trauma patients and are well equipped to handle the basic protocol of trauma response and life support. What they are not trained for is handling violence directed against them and their co-workers at the hospital itself.

Violence in psychiatric hospitals and by psychiatric patients is well covered in the literature.[4–9] A psychiatric diagnosis of mental illness has not been clearly shown to predict violent behavior,[10] however, and the American Psychiatric Association Task Force Report includes the statement, "Dangerousness must not be equated with mental illness, nor should mental illness be equated with dangerousness."[11]

Unfortunately, little has been published about violence in general hospitals by patients without diagnosed psychiatric disorders. The data we do have are from emergency physicians, internists, and family practitioners.[7,12–15] In this study, we polled a group of physicians—surgeons—who deal with victims and perpetrators of violence on a daily basis. We asked who commits violent acts, why the violent acts are committed, and when, where, and how they are committed. We reviewed the literature to provide a background for this study and to compare the prevalence of violence against surgeons

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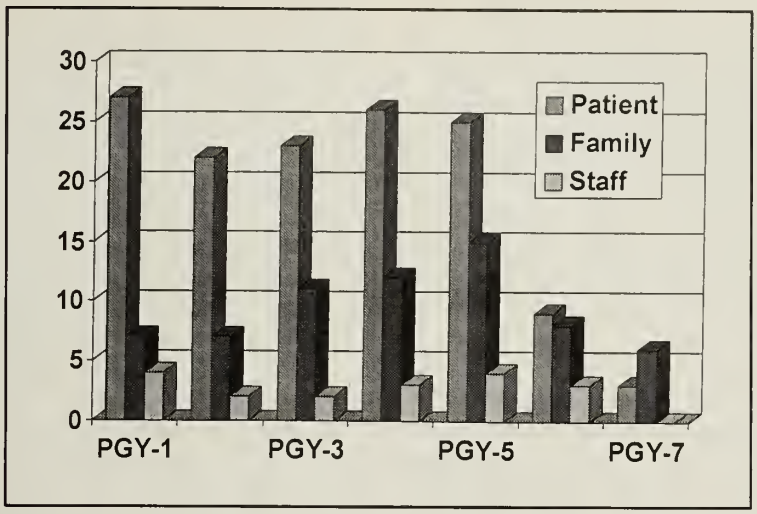

Figure 1.—The number of surgical residents who reported being attacked by patients, patient family members, and hospital staff.

with violence against practitioners in other medical specialties. Our goal is to help health care workers better understand the antecedents to violence so that they may be better able to control the outcomes.

Methods

Numerous violent attacks against residents in a training program in Louisiana prompted the survey. Its purpose was to evaluate trends and make comparisons with other training programs.

The surveys included the following elements. A section on demographics elicited data about sex, age, race, postgraduate year, and type and location of program. The second section asked whether the surgeon was ever attacked, whether the attack was verbal or physical, and whether he or she had ever witnessed an attack or felt threatened on hospital property. Other questions included whether hospital security was ever called to intervene in an altercation, who was most likely to call security, and whether security personnel carry guns. Several other questions covered the topic of guns in the hospital environment, such as who carries them (staff, patients, and surgeons, as well as security). Finally, we asked for demographic data on the perpetrators of violence and where in the hospital the violent acts occurred. The final section of the survey was reserved for comments.

We sent the surveys to surgical residents and staff at 206 teaching facilities in the US. At least one program per state was polled, including private, university-based, and military teaching programs. We received responses from 475 residents in 57 different residency programs.

We compiled the data and assessed statistical significance and trends using either Student's *t* test (for comparison of data) or an *F* test.

Results

Of the teaching programs surveyed, 28% responded, for a total of 475 responses. Positive responses (those who reported being the victim of physical violence) comprised 38% (n = 179) of the total, and negative responses, 62% (n = 296). Two hundred and eighty physicians (59%) reported having witnessed a physical attack. Five residents (1%) reported no fear of attack—that they were at "safe" institutions. Of the other 470 respondents, 51% (n = 239) reported being verbally threatened; 49% (n = 231) did not. Almost 20% of the 179 residents who reported being a victim of violence reported several instances during their training. Junior residents (postgraduate years 1–4) were more likely to be attacked than senior residents (≥5 years) ($F_{6467} = 3.97$, $P = 0.04$) (Figure 1).

Ninety women (19%) and 385 men (81%) responded; ages ranged from 26 to 40 years. The majority of the respondents were from university-based programs (59%; n = 280); 36% (n = 173) from private programs; and 5% (n = 22) from military programs. More than half of the respondents (51% ; n = 240) were in a small cities (defined as population <200,000). Table 1 depicts the demographics of the responses by hospital type and size of city. Violent threats were more likely to occur in public general hospitals than in private ones ($F_{2467} = 2.92$, $P = 0.05$). No significant differences were found between attacks in public and private general hospitals ($F_{2467} = 1.16$, $P = 0.313$) or between different-sized hospitals. Attacks were more likely to occur in the emergency room than in any other section of the hospital ($F_{6467} = 5.46$, $P = 0.01$); the wards and the parking lots were next in frequency (Table 2). More women than men reported calling hospital security to intervene in a potentially violent situation ($F_{1464} = 3.901$, $P = 0.04$).

In 138 cases (63% of the 218 who identified one or more attackers), the attack was initiated by a patient, 66

Table 1.—*Demographics of Responding Hospitals*

Type of Hospital	Number of Respondents: Small City <200,000	Medium City 200,001–700,000	Large City >700,000
Private	94	58	21
University-based	137	88	55
Military	9	8	5

Table 2.—*Where Attacks Occur*

Hospital Section	Reported Number of Attacks
Emergency room	173
Floor or ward	71
Parking lot	61
Hallway	16
Clinic	12
Cafeteria	1

attacks (30%) were initiated by a patient's family member, and 14 (7%) by a staff member (Figure 1). Of the 237 attackers identified (several cases had numerous attackers), black male patients ages 19 to 30 years were more likely than any other group to commit violent acts in general hospitals ($F_{10,464} = 5.03$, $P < 0.05$) (126 black [53%], 75 [32%] white, 31 [13%] Hispanic, and 5 [2%] Asian; 218 men [92%] and 19 women). Thirty-seven attackers were under 18 years old, 138 were 19–30, 50 were 31–50, and 12 were older than 50 (Table 3).

Finally, 470 (99%) of the 475 respondents reported either that they carry a gun or that they know someone in the hospital (staff, security, other residents) who carries a gun. At least six accidental firings of guns—for example, a gun falling out of a locker and discharging—by staff or residents in the hospital were noted in the comments section.

The response rate to this survey was 28%, comparable to other non-associated polls that have been completed by surgical residents and staff. The results were well distributed throughout the country (Northeast, South, Southwest, Midwest, and West Coast). The lower rate of responses by women vs by men is within expectations for surgical trainees in the US.[16]

Discussion

Reports of violence against physicians date back at least a hundred years.[17] There are few reports in the literature regarding nonpsychiatric violence, and none of them concern surgeons.[6,7,9,12,13,18] This research has added to our understanding of violence in a general, nonpsychiatric hospital setting.

One reason that researchers have proposed for increases in hospital violence is organizational downsizing. As hospital staffs become smaller, patient frustration and violence increase. At a large state hospital in Maryland, assaultive injuries to staff quadrupled as the number of beds was reduced by 30–40% between 1980 and 1989.[19] This may have occurred because of changes in the resident population: as the number of beds decreased, the proportion of disruptive patients on all wards increased. Other possible reasons for violence are physical environment, inexperienced staff, poor interpersonal relationships among staff members, power conflicts, low morale, poor occupational therapy programs, and fear of patients.[20]

According to our survey, junior residents (postgraduate years 1–4) were more often targets of violence than senior residents. Junior residents spend more time in patient care areas, wards, emergency rooms, and clinics and are most likely to be the first clinician to meet the patient for evaluation. Also, with experience may come safety—senior residents may develop mechanisms of defusing potentially violent situations.

Kinzel has studied the sensitivity of certain individuals to close physical encounters and demonstrated the extreme sensitivity of violent offenders to their "body-buffer zone." A concept originally developed by Horowitz, Duff, and Stratton, the body-buffer zone is the area surrounding each individual that represents the self-defined boundaries of "inner" vs "outer." Anxiety is triggered when someone trespasses in that zone.[21,22]

Control is a vital issue with clinicians, especially surgeons. Patients are given instructions and limits and may be lectured on their problems and behavior, and they may respond violently. Several researchers found that assaults occurred when the staff was setting limits for the patient's well-being. The most common conflict was over cigarette smoking. Five comments in our survey concerned threats made by patients when they were asked to stop smoking. One patient, smoking under a fire alarm that had been set off by the smoke, threatened to kill the doctor who asked him to put the cigarette out.

Table 3.—*Demographics of Attackers*

	Reported Number of Attacks
Age (years)	
<18	37
19–30	138
31–50	49
>50	12
Race	
Black	126
White	75
Hispanic	31
Asian	5
Sex	
Male	218
Female	19

In Lanza's report, in most cases, the perpetrator swore, issued demands contrary to the staff member's requests, and made threats.[23] Assaultants had poor impulse control and loud voices. Weapons were more often involved in violent acts at psychiatric hospitals (44%) than in public (24%) or private (15%) general hospitals; the kinds of weapons differed, probably due to the search of the patient's belongings prior to psychiatric admission. Weapons commonly included guns or knives (3.7–13%) or room furnishings (4–40%).[24]

The emergency department and wards were most often the settings for assault in our survey. Indeed, most violence has been reported in emergency rooms or other settings that maximize human contact.[25,26] Because of varying data collection methods, it is difficult to compare our data with those of other subspecialties, but across the board, the emergency medicine field has the largest problems with assault—72% of respondents from emergency medicine reported an attack on staff in the last five years.[27] Almost 50% of psychiatric residents reported being assaulted during their careers.[13] Medicine residents reported a 16% assault rate, many reporting multiple assaults. Family practitioners reported a 3.3% assault rate.[14]

With the data we and others have gathered, some guidelines for dealing with violence in the hospital, as well as preventing it, can be offered.

The most important task to be accomplished after an assault is a report of exactly what occurred. Two hundred and three assaults on 800 nursing staff members occurred during 1 year in a state hospital. The investigators estimated that there were five times as many assaults that went unreported.[28]

Lanza developed an instrument called the Assault Response Questionnaire, a comprehensive survey to be filled out several days to a week after the assault. The survey can be mailed to a victim or can be administered by an interviewer. This instrument can assist hospitals to identify trends and perhaps develop a training program that is responsive to employees' needs.[24] At the Royal Victoria Hospital in Montreal, an employee care program was implemented in 1982. They named a task force to address problems of security, rapidly tranquilizing patients, forming a crisis team, gathering statistics on patient violence, and training staff in the handling of aggressive patients. This team developed a protocol on the management of staff members who are physically abused. Such a program not only assists employees but also encourages a healthier work atmosphere.[21]

In the first study of its kind, Carmel and Hunter found that the level of the ward staff's compliance with mandated training in management of assaultive behavior was associated with the rate of staff injury from inpatient violence.[29] The high-compliance wards experienced much lower instances of injury than the low-compliance wards. This suggests, of course, that employees may benefit from training programs that assist them in handling assaultive behavior.

Another important aspect of violence in hospitals is the cost to the hospital after the violence occurs. Researchers estimate cost of violence to range from $38,000 to $766,290 per year.[7,29] These costs further illustrate the need for training programs to decrease and eliminate violence in hospitals.

Conclusions

There are now many additional avenues of research to be pursued. Perhaps characteristics of potential attackers should be investigated in order to understand what leads to attacks and how they can be prevented in the future. There should also be future research about what is done after an attack—report procedures and services offered to a victim. Potentially a crisis team may be established to gather statistics on patient violence and train staff, especially junior residents, in the handling of aggressive patients. With increased violence in the workplace being reported nationwide,[30] hospital personnel, including physicians, need to be aware of the potential for violence.

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Topical Lidocaine Adrenaline Tetracaine (LAT Gel) Versus Injectable Buffered Lidocaine for Local Anesthesia in Laceration Repair

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The objective of the study was to compare topical lidocaine adrenaline tetracaine (LAT gel) with injectable buffered lidocaine with epinephrine regarding pain of application or injection and anesthesia effectiveness. The study was a randomized prospective comparison trial in an urban emergency department. Physicians and patients ranked the pain of application, injection, and suturing according to a 10-cm visual analog scale. Sixty-six patients were entered, 33 in the LAT gel group and 33 in the injectable buffered lidocaine group. Injection was found to be significantly more painful than application of gel ($P < 0.001$). For anesthesia effectiveness, there was no difference according to patients ($P = 0.48$) or physicians ($P = 0.83$) for topical vs injectable forms. The number of sutures causing pain was not statistically different in the two groups ($P = 0.28$). In conclusion, LAT gel compared favorably with injectable buffered lidocaine for local anesthesia effectiveness and was significantly less painful to apply. It may be the preferred local anesthetic for this reason.

(Ernst AA, Marvez-Valls E, Nick TG, Mills T, Minvielle L, Houry D. Topical lidocaine adrenaline tetracaine (LAT gel) versus injectable buffered lidocaine for local anesthesia in laceration repair. West J Med 1997 August; 167:79–81)

Anesthetics are known to be painful to inject.[1,2] Buffered solutions that adjust the pH of commercially available anesthetic solutions have been shown to decrease the pain of infiltration.[3,4] In a previous comparison trial of four injectable anesthetics, lidocaine with epinephrine was found to be more effective for anesthesia than that without epinephrine.[5] Topical lidocaine adrenaline tetracaine (LAT gel) has been compared with tetracaine adrenaline cocaine and found to be effective in children with lacerations of the face and scalp,[6] and a liquid form of topical LAT was found to be effective in adults compared with tetracaine adrenaline cocaine.[7]

Methods

This study, which was prospective and randomized, was approved by the institutional review board. The primary endpoints were patient and physician perception of application or injection pain and anesthesia effectiveness.

The study was performed in an urban emergency department. A convenience sampling of patients who had simple lacerations were entered in the study. Patients were eligible if they were age 5 years or older with simple linear lacerations 1.5–10 cm long. Patients were excluded if they were allergic to amides or esters; if there was suspected alcohol or drug use, altered mental status, pregnancy, or glaucoma; if they did not wish to participate in the study; if the location of the laceration involved possible vascular compromise; or if the wound was more than 8 hours old.

The topical solutions (LAT gel) were prepared in December 1995 by a pharmacist. The injectable solutions (buffered lidocaine with epinephrine) were prepared one or two at a time by one of the authors of the study. All solutions were stored at room temperature, the gels in 5-cc syringes with stoppers and the injections in 10-cc syringes. The doses of anesthetic were numbered 1–66 according to a computer-generated random table of numbers prepared before the study. The injectable buffered lidocaine solutions were prepared by mixing 1 cc of 8.4% $NaHCO_3$ with 9 cc commercially prepared 1% lidocaine with epinephrine. The total volume available was 10 cc. The topical gel was prepared as 4% lidocaine, 1:2000 epinephrine, and 0.5% tetracaine in a gel form (hydrox-

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ABBREVIATIONS USED IN TEXT
LAT = lidocaine adrenaline tetracaine

yethyl cellulose) with preservatives. The gel was prepared by a pharmacist from dried ingredients mixed with water and added to the hydroxyethyl cellulose gel. The total volume of each gel was 3 cc. Because of the obvious differences in form and application, physicians and patients were not blinded to the form of anesthesia.

All personnel performing suturing were oriented to the protocol of slow infiltration with a 25-gauge needle. LAT gel was applied with a cotton swab in and up to 1 cm around the wound edge, and the gel was left in place for 10 minutes. If the patient was still sensitive to pinprick after 10 minutes, the gel remained another 10 minutes. If the patient was still sensitive, 1% lidocaine was added. The pain of application was determined after anesthetic was applied or injected and before suturing began.

Laceration repair was performed by one of the study authors, resident physicians, or nurse practitioners oriented to the study protocol. The length of the laceration, location, length of time anesthesia lasted, amount of anesthesia used, necessity for additional lidocaine, and treatment success or failure were recorded at the time of the procedure, along with any complications.

Patients and physicians ranked the pain of injection or application and the pain of suturing (anesthesia effectiveness) using a previously validated linear visual analog scale[8] so that each laceration had four associated measurements of pain. Each visual analog scale was a horizontal line graph 10 cm long with the words "no pain" at the left end and "worst pain" at the right end. Thus a score of 10.0 cm represented the most severe pain. The scale was shown to the patient before starting the procedure to familiarize the patient with the study protocol and use of the scale. Patients were followed by telephone, return visits to the emergency department, and medical records.

The a priori analysis determined that 66 patients were needed to have a power of 0.9 to detect a 1.2-cm difference in visual analog scale readings.

Results

The data were analyzed after 66 subjects were entered in the study, including 13 children ages 5 to 17. Thirty-three subjects received LAT gel and 33 received injectable buffered lidocaine with epinephrine. The number requiring further anesthesia was two in the LAT gel group and none in the injectable group (too few to apply statistical analysis). In one of the two needing further anesthesia, the gel was not allowed to remain in place after 10 minutes of application as per protocol, and the scores for this entry were excluded from the calculations.

There were differences between the LAT gel and injectable buffered lidocaine groups in two areas of demographics, sex and amount of local anesthesia used. There were statistically fewer females in the LAT gel group ($P = 0.027$). More volume of solution was used in the injectable buffered lidocaine group ($P < 0.001$). Mean age, length of lacerations, and location of lacerations were approximately equally divided for the LAT gel vs injectable buffered lidocaine group. These results are summarized in Table 1.

Table 1.—*Demographics*

	LAT Gel	*Injectable Lidocaine*	*P Value*
Sex (M/F)	5/28	13/20	0.027*
Age (years)	29	30	0.36*
Length of laceration (cm)	2.3	2.5	0.87*
Initial amount of local anesthesia (cc)	1.7	4.6	0.06*
Need for more anesthesia (n)	2	0	
Location of laceration (n)			
Extremity	13	11	0.23†
Face	17	13	
Scalp	3	7	

Results are means.
*Wilcoxon rank sum test.
†χ^2 test, extremities vs face and scalp.

Topical lidocaine application was significantly less painful than injection of lidocaine according to both patients and physicians ($P < 0.001$) (Table 2). For suturing (anesthesia effectiveness), patients and physicians found no difference between LAT gel and injectable buffered lidocaine ($P = 0.83$ physicians and $P = 0.48$ patients) (Table 3). The number of sutures causing pain according to patients, another measure of anesthesia effectiveness, was calculated as a percent (Table 4). There was no difference in LAT gel vs injectable buffered lidocaine in the percent of sutures causing pain ($P = 0.28$).

Because of the difference in numbers of females between the two groups, we compared measures for males vs females. Using χ^2 analysis, we found no differences in demographics ($P > 0.05$). For physician and patient pain scores during suturing, sex and treatment group were not significantly different for the topical vs injectable group. There was a difference in males vs females with injection pain according to physicians, with females having greater pain than males ($P = 0.015$).

Table 2.—*Physician and Patient Rating of Pain of Local and Topical Anesthetic Application (Visual Analog Score)*

	LAT Gel	*Injectable Lidocaine*	*P Value*
Median (interquartile range)			
Physician rating	0 (0–0)	1.4 (0.45–3.45)	0.001
Patient rating	0 (0–0.15)	1.2 (0.15–2.75)	0.001

P values were determined using Wilcoxon rank sum test.

Table 3.—*Physician and Patient Rating of Pain of Suturing (Visual Analog Score)*

	LAT Gel	Injectable Lidocaine	P Value
Median (interquartile range)			
Physician rating	0 (0–0.55)	0 (0–0.35)	0.83
Patient rating	0 (0–1.35)	0 (0–0.6)	0.48

P values were determined using Wilcoxon rank sum test.

Table 4.—*Percent of Sutures Causing Pain, per Patient*

	LAT Gel	Injectable Lidocaine	P Value
Mean (%)	13	6	0.28
Median (interquartile range)	0 (0–18)	0 (0–0)	

P values were determined using Wilcoxon rank sum test.

The mean score for injections for males was 1.4, and for females, 2.8. For females, LAT gel was significantly less painful to apply than buffered lidocaine was to inject. The mean scores for application for LAT gel for females was 0, and for males, 0.3.

To determine effectiveness of LAT gel vs injectable buffered lidocaine at extremity locations, a comparison was made for laceration scores at extremity locations vs face and scalp. Using Wilcoxon's rank sum test, we detected no difference in physician application (P = 0.49), patient application (P = 0.87), or physician suturing (P = 0.17) for extremity lacerations in the two groups. For patient suturing, the difference for extremities (median score 1.2; mean score 2.4) vs face and scalp (median score 0; mean score 0.3) was nearly significant (P = 0.052).

Follow-up was available in 75% of the patients, with equal rates in the topical and injectable groups. No complications or wound infections were reported.

Discussion

In previous studies of topical anesthetics, there is no mention of pain or discomfort of application.[6,7,9–12] In this study, we compared an injectable anesthetic with LAT gel to determine differences in application or injection pain and to determine if LAT gel was as effective an anesthetic as an injection. Previous studies have compared topical LAT to tetracaine adrenaline cocaine,[6,7,12] but comparison has never been made to injectable anesthetics. We chose injectable buffered lidocaine with epinephrine because we have found that solutions with epinephrine are preferred for anesthesia effectiveness. We speculate that this is because vasoconstrictor action keeps anesthesia localized to the wound site.[5] Our power was 0.9 to detect a 1.2-cm difference in readings of a visual analog scale. This difference is consistent with the minimum clinically significant difference according to a previous study.[13]

We detected a difference in application or injection pain, with LAT gel being significantly less painful to apply. Patients and physicians preferred LAT gel for this reason. This factor may be especially important in children, in whom ease of laceration repair depends on cooperation. Other uses are in lacerations requiring plastic repair—topical anesthetics do not distort tissues during repair. Another advantage is less needle exposure for health care personnel.

There were significantly fewer females in the LAT gel group. With further analysis of the results of the study, no difference in pain scores was found, except application pain according to physicians for male vs female patients. Whether there is a difference in perceived pain from laceration repair in females vs males is unknown.

The difference in anesthetic effectiveness in extremities vs the face and scalp approached statistical significance. Previous studies have shown that topicals are less effective at extremity sites, perhaps because of less vascularity than the face and scalp.[10,11] Further study of the use of LAT gel in extremities is needed.

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Articles

Pathophysiology of the Thalassemias
The Albion Walter Hewlett Award Presentation

STANLEY L. SCHRIER, MD, *Stanford, California*

The Albion Walter Hewlett Award (named for Professor of Medicine and Chair of the Stanford Department of Medicine 1916–1925) recognizes a role model, accomplished in discovery of the biological sciences and at the same time a consummate and compassionate physician. In introductory remarks, Dr. Stanley L. Schrier, Professor of Medicine (Hematology), the tenth recipient of the Award, indicated that the person so identified is no longer a viable model in academic medicine. The loss of this sort of person is serious because this appropriately trained physician-investigator was uniquely positioned to study pathophysiology, defined as the processes by which disordered biology produces disease. He used his own studies on the clinical manifestations of the thalassemias to clarify what he meant by pathophysiology. Thus he and his colleagues first defined membrane material properties of α and β thalassemic RBC membranes and the states of hydration of α and β thalassemic RBC and found them to be strikingly divergent. The biochemical counterparts of these alterations proved to be the accumulation of the excess unmatched partially oxidized globin chains on the membrane skeleton. In vitro studies with chemical oxidants selectively oxidized α and β globin chains which then attached to the RBC membrane skeleton and reproduced the membrane material properties characteristic of β and α thalassemia respectively. Many of these alterations had occurred prior to the reticulocyte stage so that pursuit of pathophysiology shifted to studies of marrow erythroid precursors, and it was shown that in β thalassemia major there was accelerated programmed cell death as well as defective assembly of the membrane skeleton.

(Schrier SL. Pathophysiology of the thalassemias—the Albion Hewlett Award Presentation. West J Med 1997 August; 167:82–89)

Introduction of Dr. Schrier by Lawrence Leung, M.D., Chief of the Division of Hematology, Stanford University School of Medicine.

Today we are here to honor Dr. Stanley Schrier, the winner of the 10th Annual Albion Walter Hewlett Award. The award was established in 1983. It recognizes a Stanford physician who demonstrates a combination of outstanding skills in developing and applying scientific knowledge as well as great sensitivity and compassion for caring for patients. It is presented in memory of Albion Walter Hewlett, who died an untimely death in 1925. Dr. Hewlett was Chairman of the Department of Medicine from 1916–1925.

Stanley Schrier received his MD from Johns Hopkins in 1954. After his housestaff training at Hopkins and fellowship training in hematology at the University of Chicago, he came to Stanford in 1959 as an instructor of medicine. He rose through the ranks rapidly and was Chief of Hematology from 1968–1994. Dr. Schrier was Chairman of the American Board of Internal Medicine Committee on Hematology from 1984–1988. He organized the education program for the American Society of Hematology in 1993, and in 1996 he was the Chairman of the Association of Hematology and Oncology Training Program Directors. He received the Kaiser Teaching Award, here at Stanford, three times. In 1982 he also received the David Rytand award for Excellence in House Staff Clinical Teaching. Dr. Schrier has a long and productive research career. He has held an NIH RO1 grant for 36 consecutive years. His research has been focused on the red cell membrane and its abnormalites. He has published 115 papers.

* * *

I would like to take this opportunity to thank all of you, my friends and my colleagues, and in particular Mr. William Hewlett and the Hewlett family for making this award possible. I am very touched.

The adult erythrocyte, or red blood cell, is a biconcave disc that has 40% more surface area than a sphere

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of comparable volume. This excess surface area allows erythrocytes with a 7-8 micron diameter to deform and elongate and thereby squeeze through 2-micron pores in the splenic cords and 3-micron capillaries where a full, plump sphere could not. The erythrocyte carries hemoglobin composed of two alpha chains and two beta chains, each carrying its own heme molecule. Each heme has an iron atom which allows that molecule to pick up oxygen in the lungs, carry it to the tissues, and offload it. Carrying hemoglobin in this form is the major function of the erythrocyte. The assembly of hemoglobin is miraculous: The genes for alpha globin are on chromosome 16, while the genes for beta globin are on chromosome 11. Heme is synthesized partly in mitochondria, partly in cytosol, and it all comes together in the synthesis of normal adult human hemglobin A, $\alpha_2\beta_2$. The ratio of alpha to beta chains is 1±.05. Synthesis of hemoglobin is very tightly controlled.

Why all this interest in red blood cells? Part of my story began approximately 5,000 to 8,000 years ago when we human beings stopped being hunter-gatherers and became pastoralists or agriculturists. Agriculturists settled down and built cities and began raising crops. They quickly determined the need for a stable supply of water, and this meant irrigation. In turn, irrigation led inevitably to stagnant pools of water that allowed mosquitoes to breed. Mosquitoes carry malaria parasites, the primary target of which is the erythrocyte. The pressure of malarial infection was so profound that in under 200 generations, virtually all of the genetically determined erythrocyte abnormalities arose.[1] They are as variable as the sickle gene, which in the heterozygous state is protective against *falciparum* malaria while the homozygous state results in sickle cell anemia. The hemoglobin C variant is similar, and sub-Saharan Africans have lost their Duffy antigen because it is the docking site for the *vivax* malaria parasite. The most common erythrocyte abnormality that evolved to mitigate the consequences of malaria was the thalassemias. In these disorders the tightly controlled and coordinated synthesis of alpha and beta globin chains is altered, leading to an imbalance. For reasons which are still obscure, this imbalance, in the heterozygous state, protects against the ravages of malaria. However, the consequences of this imbalance were quite significant. Because of reduced synthesis of either alpha or beta globin there was less hemoglobin per cell and this led to hypochromia, microcytosis, and variable anemia. Decreased synthesis of alpha globin leads to alpha thalassemia and decreased beta globin synthesis results in beta thalassemia. In addition to poor synthesis of hemoglobin there is accumulation of the excess unmatched other chains, and this chain accumulation somehow causes the affected erythrocyte to be prematurely removed from the circulation (hemolysis). Perhaps more important, at least in the beta thalassemias, the accumulation of these unmatched globin chains damages the marrow erythroid precursors, leading to their intramedullary lysis or ineffective erythropoiesis. These processes can be trivial in some cases but

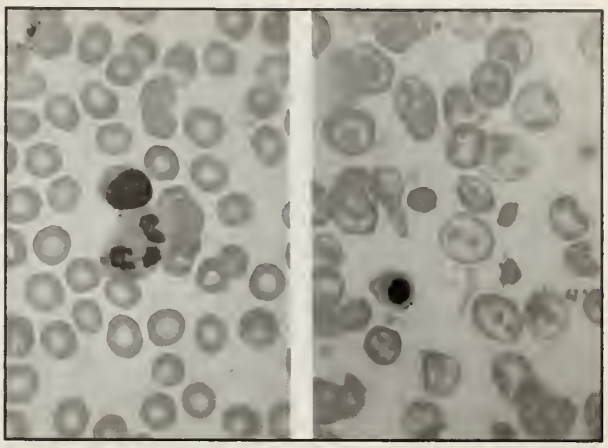

Figure 1.—Smear of normal RBC on the left and β thalassemia intermedia RBC on the right. In addition to the well-known hypochromia and microcytosis, note the very abnormal RBC shapes in β thalassemia RBC.

very important in other cases by producing severe and even fatal anemia. Patients with Cooley's anemia (beta thalassemia major) are absolutely dependent on red blood cell transfusions. With each transfusion, iron is delivered; with time it accumulates in the liver and the heart eventually leading to a death from hemochromatosis. The biologic question then was: how does the accumulation of excess globin chains cause the hemolysis and ineffective erythropoiesis? A hematologist starts with the peripheral smear.

Not only are these thalassemic RBC poorly hemoglobinized but they have very abnormal shapes (Figure 1). These abnormal shapes are a clue that something very serious may have gone wrong with the membrane. This led to initiation of a systematic study of the mechanical properties of these cells and their membranes. Dr. Mohandas Narla co-invented the ektacytometer which allows one to look at mechanical properties of erythrocytes. One can apply incremental shear stress to a suspension of RBC and measure the resulting elliptical deformation. This provides an accurate measure of RBC deformability. Alpha and beta thalassemic RBC are both very rigid when analyzed in the ektacytometer. One can also make a membrane preparation of erythrocytes by taking out the hemoglobin and subjecting these membranes to increasing shear stress to see where the membrane structure fails and the membranes fragment. In a striking and reproducible manner beta thalassemic membranes failed quickly and therefore were mechanically unstable. We then studied alpha thalassemia (Hgb H disease) and found that the membranes were hyperstable (Figure 2).[2] We proceeded to study the density of erythrocytes and thus determine their state of hydration. The deformability characteristics of RBC are quite dependent on their internal hemoglobin concentration, which in turn is measured by the density. The density of RBC is primarily determined by their contents. Normally two-thirds of the volume of RBC is water and one-third is hemo-

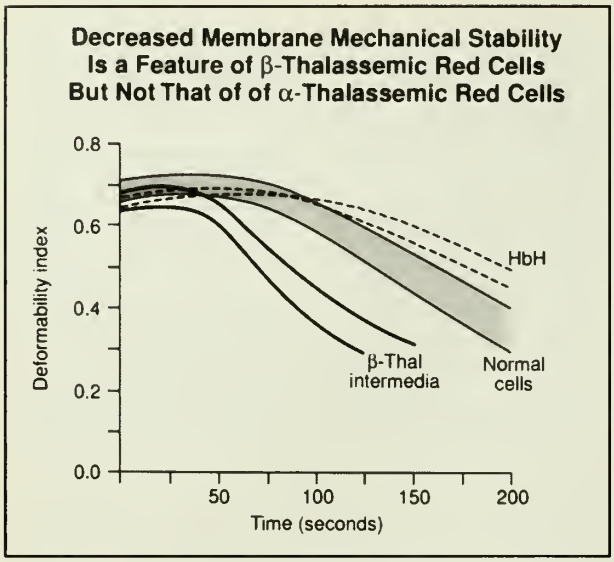

Figure 2.—RBC membrane stability. Membranes were prepared from normals (shaded zone) and patients with severe α and β thalassemia and then subjected to high shear stress in the ektacytometer. When the membrane structure fails, the membranes fragment and the curve sharply drops. β thalassemia intermedia membranes are unstable when compared to normals while α thalassemia (HbH) disease are hyperstable.

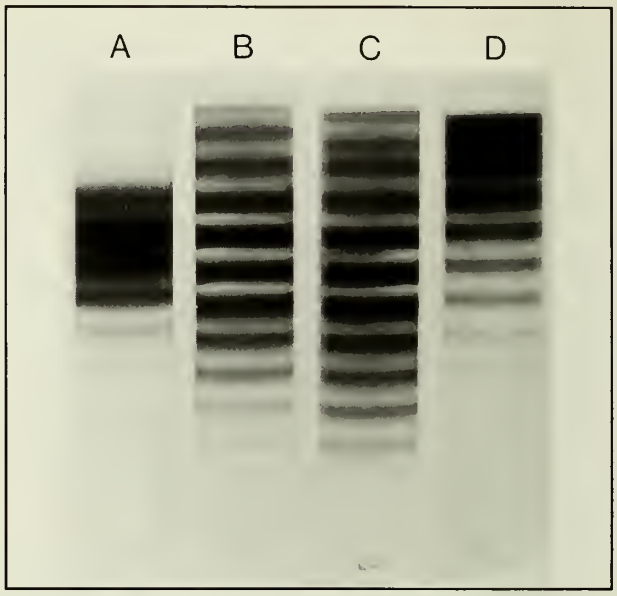

Figure 3.—Density gradient analysis of RBC. RBC from a normal subject (**A**), a patient with severe α thalassemia (HbH) (**D**) and two patients with β thalassemia intermedia (**B, C**), one splenectomized (**C**), were separated on discontinuous Stractan gradients. The lighter fractions including reticulocytes are on top of the gradient. Note that in α thalassemia (**D**) there is a distinct shift to lighter (less dense populations) way out of proportion to the 3% to 5% reticulocyte count. These cells are overhydrated. In contrast note that in β thalassemia intermedia (**B,C**) while there are some light populations representing reticulocytes, there are very dense populations representing cells that are clearly dehydrated.

globin. The hemoglobin concentration determines the cell's density. Since there is less hemoglobin in thalassemic RBC, it was thought that the RBC would be less dense or lighter than normal (Figure 3). In alpha thalassemia (HbH) the erythrocytes are, as anticipated, uniformly overhydrated. In contrast beta thalassemic erythrocytes have some well hydrated forms, but there are large populations of very dehydrated, very rigid, very viscous erythrocytes as dehydrated as RBC in sickle cell disease. Therefore, there are at least two ways in which alpha and beta thalassemic RBC differ: overhydration in alpha thalassemia and dehydration in beta thalassemia; membrane mechanical hyperstability in alpha thalassemia, contrasted with instability in beta thalassemia.[2]

What are the biochemical counterparts of these events? It had been known for many years that there was too much globin in thalassemic erythrocyte membranes. So the following questions were proposed: Under the hypothesis that this globin might be causing the trouble, where in the membrane was the globin located? What was it? Was it hemoglobin, was it alpha chains, was it beta chains? What was the state of the globin? Was it oxidized?

The erythrocyte membrane contains an asymmetric phospholipid bilayer core, and two kinds of proteins make up the membrane. Transmembrane proteins are hydrophobic because they cross the phospholipid bilayer. The major one is called band-3. These proteins provide vertical stability to the membrane. In contrast, there are proteins on the cytosol face of the membrane that comprise the membrane skeleton. They are extensively crosslinked, forming hexagonal structures that allow the erythrocyte to be deformed, but then undergo elastic recoil. One can actually dissect the membrane proteins into transmembrane-rich fractions and skeleton-rich fractions. It was thought likely that the globin attached to the membrane would be bound to band 3 because it has binding sites for hemoglobin. When transmembrane protein-enriched preparations were analyzed, the globin was not there; it was in the membrane skeletal preparations (Figure 4).[3] Normal skeletons (A) have a delicate cross-linked lattice, while the beta thalassemia skeletons show huge accumulations of globin with coarse lattice formation. The biochemical analysis of these skeletal preparations of alpha and beta thalassemic RBC showed large amounts of globin. Therefore the answer to the first question was that the membrane-bound globin was primarily attached to its skeleton.[3,4]

The next question was, what was that globin? Was it unmodified hemoglobin? Was it alpha/beta dimers or was it the excess unmatched globin chain? Triton-acid-urea gel electrophoresis cleanly separates the different globin chains. The membrane preparation in severe beta thalassemic RBC showed a great excess of alpha, a little bit of beta, and a little bit of γG . (There are two gamma chains γA and γG that go to make hemoglobin F or fetal hemoglobin.) When the skeletons were analyzed, there

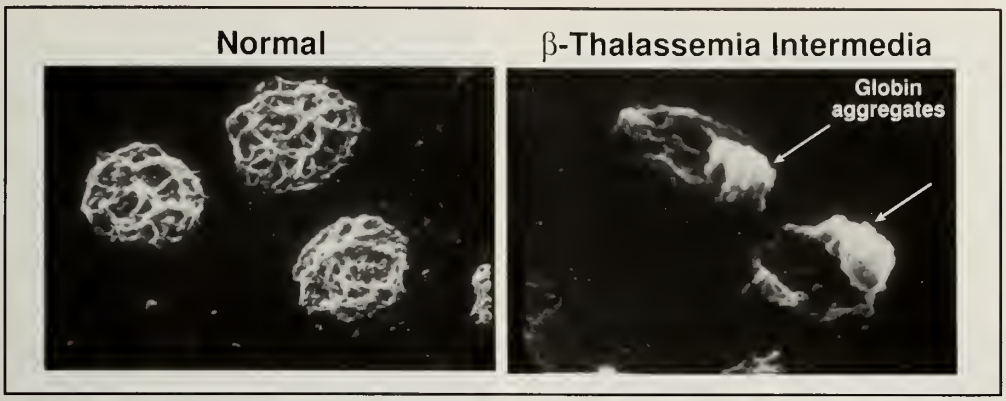

Figure 4.—Scanning electron microscopy of isolated membrane skeletons prepared by triton extraction of whole membranes followed by sucrose density gradient separation. Normal skeletons are on the left and β thalassemia intermedia skeletons are on the right.

was virtually only alpha globin. The same sort of analysis on alpha thalassemia (HbH) RBC showed that there were only beta chains attached to the membrane skeleton.[3,4] The answer to the second question was that the globin attached to the membrane skeleton was the excess unmatched globin chain.[4]

The next question was whether the membrane-associated globin was altered in any way. Thiol-disulfide exchange chromatography was used to assay oxidation of globin and other proteins. If a protein becomes extensively oxidized, it loses its thiols and does not stick to an activated thiol column. In RBC from both alpha and beta thalassemia, there is a large amount of oxidized globin present on the RBC membrane.[4]

A summary of this work is as follows: In the thalassemias, large amounts of globin were attached to the membrane, primarily to the skeleton. It was the unmatched excess globin chain, alpha in beta thalassemia, beta in alpha thalassemia, and the globin had undergone partial oxidation. When globin is attached to the membrane, it carries a heme with its iron, each of which can induce the generation of reactive oxygen species. These in turn could oxidize adjacent membrane proteins and produce the instability or hyperstability and

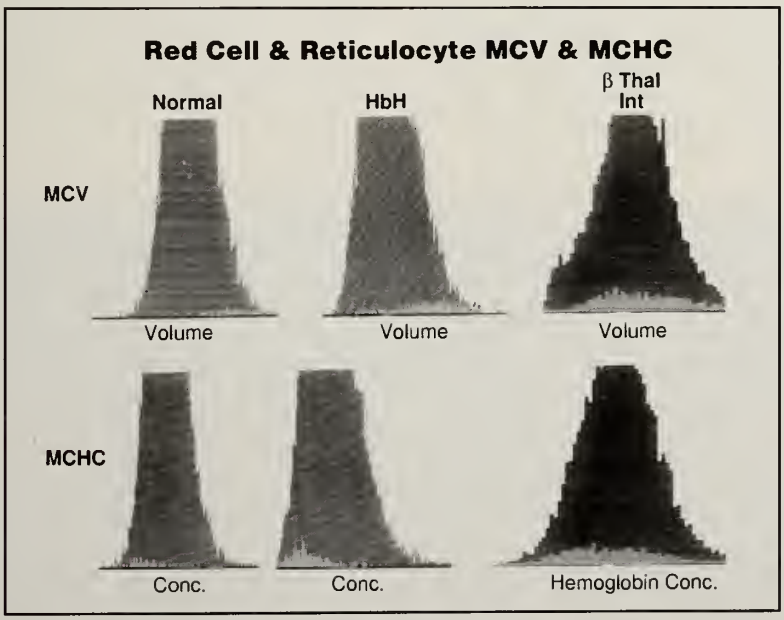

Figure 5.—The Bayer Technicon H*3 automatic RBC analyzer provides a cell by cell measurement of MCV, MCH, and MCHC of RBC and reticulocytes in the sample. The reticulocytes appear as very light shade at the bottom of the display. The key points are that in severe α thalassemia (HbH) the reticulocytes are overhydrated (high MCV and low MCHC) as they leave the marrow, while in β thalassemia intermedia the reticulocytes are already variably dehydrated (populations with low MCV and high MCHC).

Table 1.—*Membrane Characteristics of Thalassemic Red Cells and Oxidized Normal Red Cells*

	Membrane Properties		
	Deformability	*Mechanical Stability*	*Membrane Skeletal Associated Globin*
α thalassemia	Rigid	Hyperstable	Predominantly β globin
Methylhydrazine-treated normal red cells	Rigid	Hyperstable	β globin
β thalassemia	Rigid	Unstable	α globin
Phenylhydrazine-treated normal red cells	Rigid	Unstable	α globin

the associated changes in cellular hydration that were observed.

It was important to determine if these changes could be reproduced using a chemical attack. Normal erythrocytes were incubated with two oxidants, phenylhydrazine and methylhydrazine. Phenylhydrazine caused increased membrane instability. In contrast, methylhydrazine produced membrane hyperstability. Biochemical analysis showed that phenylhydrazine caused oxidized alpha globin to bind to membrane skeletons while methylhydrazine caused oxidized beta globin to bind to the membrane skeletons.[5] Table 1 shows the distinct parallel between the sort of oxidized globin chain bound to the membrane and membrane mechanical stability or instability. Thus, virtually each globin chain attached to the membrane produces a unique pathophysiology.

At this point in our studies on the pathophysiology of the thalassemias we recalled the ferrokinetic observations made in the 1970s. When ^{59}Fe is injected intravenously it is incorporated into hemoglobin, first accumulating in the marrow erythroid precursors. About 7 to 10 days later, the iron now incorporated into RBC hemoglobin leaves the bone marrow and normally about 80% of the injected radioactive iron appears in circulating red erythrocytes. This is effective erythropoeisis. When the same study was done on patients with beta thalassemia major, the iron entered the marrow, but most of it remained there. Seven to 10 days later, only 20% of that iron was incorporated into erythrocytes which means that approximately 60% of the cells had died in the bone marrow.[7,9] This observation caused us to refocus attention on the marrow as a site of

Figure 6.—Laser confocal fluorescence microscopy of erythroid precursors isolated from the marrow of patients with Cooley's anemia and then reacted with a specific monoclonal antibody to α globin chains visualized by combined fluorescence and Nomarski microscopy. Note the very large aggregates of α globin that appear even in the earliest erythroid precursors, the proerythroblasts, identified by their large diameter (12-15μ).

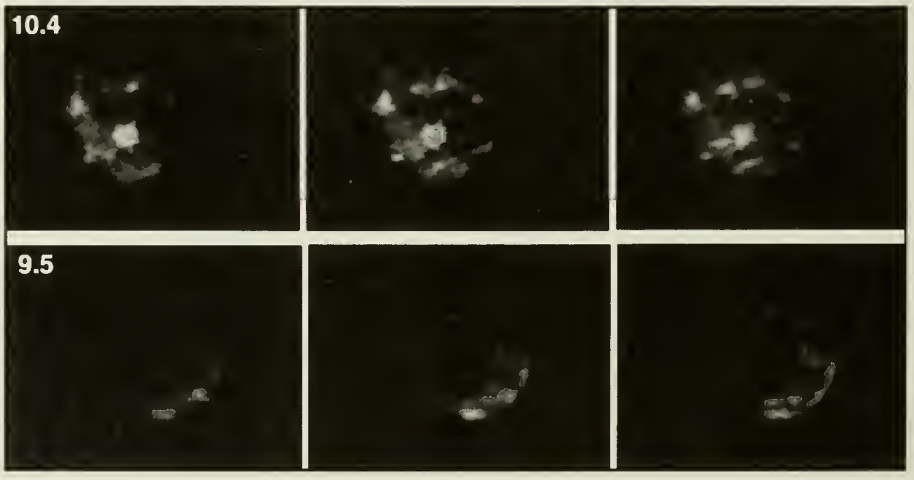

Figure 7.—Assembly of band 4.1 into the membrane of β thalassemia major erythroid precursors. Three sections through the equator at 0.5-micron serial cuts are shown for two polychromatophilic erythroid precursors of diameter 9.5 and 10.4μ. By laser confocal fluorescence microscopy note the clumping, irregular rim fluorescence and coarse deposits in the cytoplasm and nucleus.

the major damage at least in beta thalassemia. In the Bayer Technicon H*3 cell analyzer which displays MCV, MCH, and MCHC simultaneously for adult RBC and reticulocytes, it can be seen that when normal reticulocytes leave the marrow they are well hydrated. In beta thalassemia the reticulocytes are already variably dehydrated. In HbH disease the reticulocytes are already clearly overhydrated (Figure 5). Therefore changes identified in alpha and beta thalassemic RBC are substantially determined in the marrow. We realized that if we were to understand the pathophysiology of the thalassemias, we must study the bone marrow in both alpha and beta thalassemia. We were fortunate because Professor Guido Lucarelli and his associate Dr. Angelucci at Pesaro, Italy, had begun an experimental program allo-transplanting patients with severe beta thalassemia. They have now treated more than 800 patients with remarkable success such that about 80% of these patients are alive and well. As part of their protocol they obtain marrow just before transplantation and send us samples. Methods were developed to isolate erythroid precursors from the bone marrow of such patients and study them. The first question was to determine when and where the accumulation of alpha globin in beta thalassemia major erythroid precursors occurred. Using a unique monoclonal antibody to alpha globin we determined that about one-third of the erythroid precursors showed quite large aggregates of alpha globin (Figure 6) occurring even at the earliest erythroid precursor stage, the proerythroblast. Prior studies had shown that the membrane skeleton in these patients was abnormal, with membrane instability and partial oxidation of band 4.1.[4] Therefore the plan was to study two critical skeletal proteins, spectrin and band 4.1, as well as the major transmembrane protein, band 3. Using immunofluorescence along with laser confocal fluorescence microscopy, the assembly of these proteins was visualized. Normal erythroid precursors show smooth rim fluorescence for band 3, spectrin, and band 4.1 (not shown). In beta thalassemia major erythroid precursors, assembly of band 4.1 was abnormal, with collections of band 4.1 in the nucleus and a very abnormal assembly of the membrane skeleton (Figure 7). The same was true for spectrin assembly. In using the technique of immunofluorescence with the advantages of laser confocal fluorescence microscopy, we can visualize the localization of two kinds of molecules simultaneously. Thus we can identify the sites of band 4.1 assembly using a Texas red–labeled antibody which fluoresces red, and simultaneously visualize the sites of alpha globin chain accumulation using an antibody tagged with fluoresceine isothiocyanate (FITC), which fluoresces green. We can also identify sites where two molecules colocalize because the combination of red and green fluorescence produces a brilliant yellow fluorescense. Using simultaneous two-color immunofluorescence (not shown) in the thalassemic erythroid precursors, band 4.1 colocalized with alpha globin. Perhaps the oxidized alpha globin caused the oxidation of adjacent band 4.1 and thus accounted for the abnormality of the assembly of band 4.1 and of spectrin. Importantly, we never saw colocalization of alpha globin with band 3; however, there is a profound defect in band 3 incorporation into beta thalassemia erythroid precursors which is more severe in the least mature precursors (Figure 8).

These membrane abnormalities affect about one-third of the cells in Cooley's anemia, but there is 60% ineffective erythropoiesis as well. Therefore an additional process seemed likely. We thought apoptosis or pro-

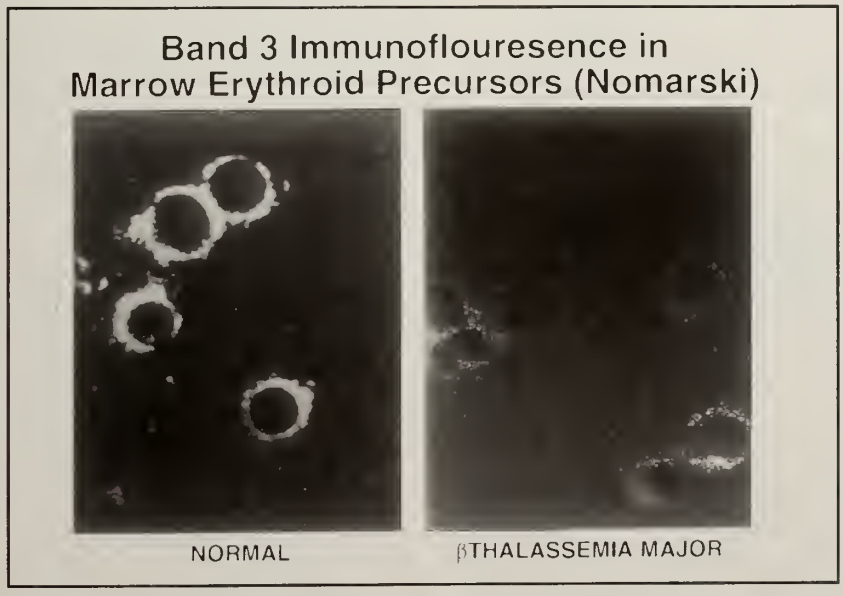

Figure 8.—Immunofluorescent staining for band 3 and Normarski microscopy in normal and β thalassemia major erythroid precursors. Note that the brightness of fluorescence is much more intense in the normal erythroid precursors.

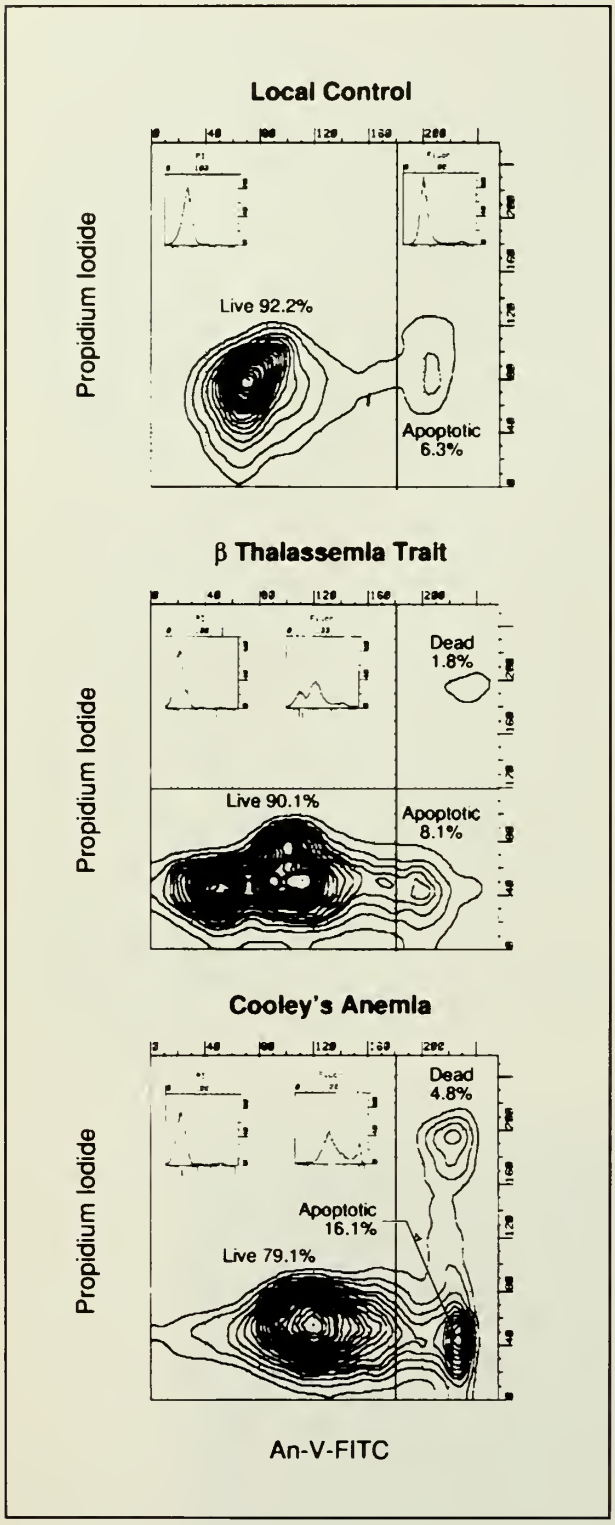

Figure 9.—Programmed cell death in erythroid precursors. This method uses FACS scanning to detect those erythroid precursors undergoing apoptosis by detecting the movement of phosphatidylserine (PS) to the outer leaflet of the phospholipid bilayer. FITC-labeled AnnexinV (An-V-FITC) specifically binds to cell membranes expressing PS on the outer surface. Note the progression in combination of apoptotic and dead precursors from the normal to the β thalassemia trait to β thalassemia major.

grammed cell death could play a role. Using the DNA ladder technique it appeared that in beta thalassemia major the erythroid precursors underwent accelerated apoptosis.[9] In order to study apoptosis in beta thalassemia and identify its cause(s) a simpler quantitative assay was needed. As part of the apoptotic process the normal asymmetry of the plasma membrane phospholipid bilayer is scrambled such that phosphatidylserine (PS), ordinarily confined to the inner leaflet, moves to the outer leaflet. One can identify this scrambling using FITC-labeled AnnexinV, which specifically binds to PS on the outer surface of cells. By FACS scanning using FITC-AnnexinV along with a label that identifies dead cells (7AAD or propidium iodide), it is possible to identify live, dead, and apoptotic erythroid precursors (Figure 9). Comparing erythroid precursors from normal, beta thalassemia trait, and beta thalassemia major there was a significant increase in dead and apoptotic cells. We currently are using this quantitative method to explore the underlying cause(s) of apoptosis in severe beta thalassemia and are beginning a parallel analysis of alpha thalassemia marrow erythroid precursors.

How far have we come? Our research has been directed by the idea that the excess unmatched globin chains play a central role in the pathophysiology of the thalassemias. In terms of therapeutic interventions, we now know enough to focus our attention on the bone marrow, but we probably knew that before. Sooner rather than later, gene replacement will be the answer, but getting the right genes into the right place under the right control mechanism is complicated. Since the pathophysiology depends on the excess of the unmatched globin chain perhaps we can stimulate specific proteases which would degrade the correct globin chain.

What else can we do? We know from human experiments that patients with severe beta thalassemia occasionally inherit alpha thalassemia as well. The anemia gets better because there is less alpha globin chain to accumulate. So we might try to suppress the normal globin chain.

Let me now come back to my earlier theme and summarize what pathophysiology means to me. I believe that the appropriate focus for research by physicians is the search for understanding of disordered human biology; I call it pathophysiology. This is what the Hewlett Award recognizes. If the search for answers about pathophysiology is not to be centered in one person, an obsolete model, cross-talk is needed between the bedside and the bench. This requires mutual respect between two cultures.

Second, what about support for research? Like anyone else in my field, I think it is inadequate. Given that it is inadequate, what sort of research is to be supported and by whom? Those of you who have been reading *The New England Journal of Medicine*'s articles on the characteristics of HMOs will recall that there is a large cash flow, some of it going to administration and to executives.[10] Importantly there is minimal support of basic research[10,11] and perhaps some support for outcome research.[12] I believe that outcome research is very important, but it is not enough. I was struck by an interview[13] with Nobel lau-

reates Drs Michael Brown and Joe Goldstein. Dr Brown responded to a question on the impact of large health care systems saying that he felt some investigators needed to be sequestered if they were to probe more deeply into biological questions. I suspect he meant sequestering from intellectually paralyzing discussions about RVUs and compliance with Medicare billing codes. Dr Goldstein said, "Take the polio example. If we didn't know how to grow viruses, isolate the polio virus, and make a vaccine, then the health care system today would be figuring out the best ways to put the largest number of iron lungs in the smallest space for the lowest cost."

What research needs to be supported? I believe we need support of research on mechanism, on pathophysiology. We were lucky. Our hypothesis seems correct. But even the best investigators will choose the wrong hypothesis to study. We must hope that funding agencies will respect the need for mid-course corrections, revision of hypotheses that leads to new discovery.

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Conferences and Reviews

The Pelvic Floor in Health and Disease

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Normal pelvic floor function involves a set of learned and reflex responses that are essential for the normal control and evacuation of stool. A variety of functional disturbances of the pelvic floor, including incontinence and constipation, are not life threatening, but can cause significant distress to affected patients. Understanding the normal anatomy and physiology of the pelvic floor is essential to understanding and treating these disorders of defecation. This article describes the normal function of the pelvic floor, the diagnostic tools available to investigate pelvic floor dysfunction, and the etiology, diagnosis, and management of the functional pelvic floor disorders that lead to incontinence and constipation.

(Shelton AA, Welton ML. The pelvic floor in health and disease. West J Med 1997 August; 167:90–98)

Normal Anatomy and Physiology

Pelvic Floor Anatomy

The pelvic floor is a consortium of funnel-shaped muscles that separates the pelvis and the perineum. It is composed of the *levator ani* and *puborectalis* muscles. The levator ani consists of two broad, thin, symmetric muscular sheets that originate around the pelvic sidewall and in the sacrospinous ligament that forms the principal support of the pelvic viscera. The puborectalis muscle originates in the posterior aspect of the pubis, forms a sling around the rectum, and returns to the posterior aspect of the pubis. The fibers of the puborectalis are situated immediately adjacent to and below the innermost component of the levator ani muscle, where they are intimately associated with the upper posterolateral fibers of the deep external anal sphincter. Thus, the puborectalis serves as a bridge between the broad sheetlike component of the funnel created by the levator and the narrow spout of the funnel created by the external anal sphincter (Figure 1). The puborectalis in the contracted state is responsible for the normal acute anorectal angle between the levators and the external sphincters. It is also responsible for the shelf that is normally palpable between the anal canal and the rectum on digital rectal exam.[1–3] The innervation of the muscles of the pelvic floor is from branches of ventral nerve roots of S2–S4. These originate proximal to the formation of the sacral plexus and run on the inner surface of the levator ani muscles.[4]

The anal canal is the closed slit-like lowermost portion of the digestive tract. It is encircled by the internal and external sphincter muscles which, in the resting state, keep the anus closed. From its junction with the rectum, it runs downward and backward. Two different definitions of the anal canal are used, the anatomic anal canal and the surgical anal canal. The anatomic anal canal is approximately 2 cm long and extends from the dentate line to the anal verge. The surgical anal canal is approximately 2 to 5 cm long and extends from the anorectal ring created by the puborectalis at the apex of the pelvic floor to the anal verge. The surgical anal canal is important in normal anorectal function and is considered the physiologic anal canal.[3] The anal canal high-pressure zone is generated by the internal and external anal sphincters at rest and constitutes the physiologic sphincter.

The anal canal is maintained in a closed slit-like conformation by the internal and external anal sphincter. The internal anal sphincter is a condensation of the inner circular muscle of the rectum. It is about 2.5 to 4 cm long and 0.5 cm thick. It ends about 1 to 1.5 cm distal to the dentate line, proximal to the end of the external anal sphincter.[5] The internal anal sphincter is composed of smooth muscle and is innervated by the autonomic nervous system. It receives excitatory sympathetic innervation via the hypogastric nerves (L5) and inhibitory parasympathetic innervation by pelvic splanchnic nerves (S2–S4).[6,7]

The external anal sphincter forms a circular cuff around the internal anal sphincter. It is slightly longer than the internal anal sphincter. It extends from the puborectalis (from which its most cranial fibers are indistinguishable) to the anal verge, where it becomes subcutaneous. The external anal sphincter is 6 to 10 mm thick.[8] The exact anatomy of the external anal sphincter is a matter of some debate. It has been viewed as a triple loop system with deep, superficial, and subcutaneous loops. The deep loop represents the puborectalis muscle in close association with the most cranial fibers of the external sphincter. The superficial component encircles

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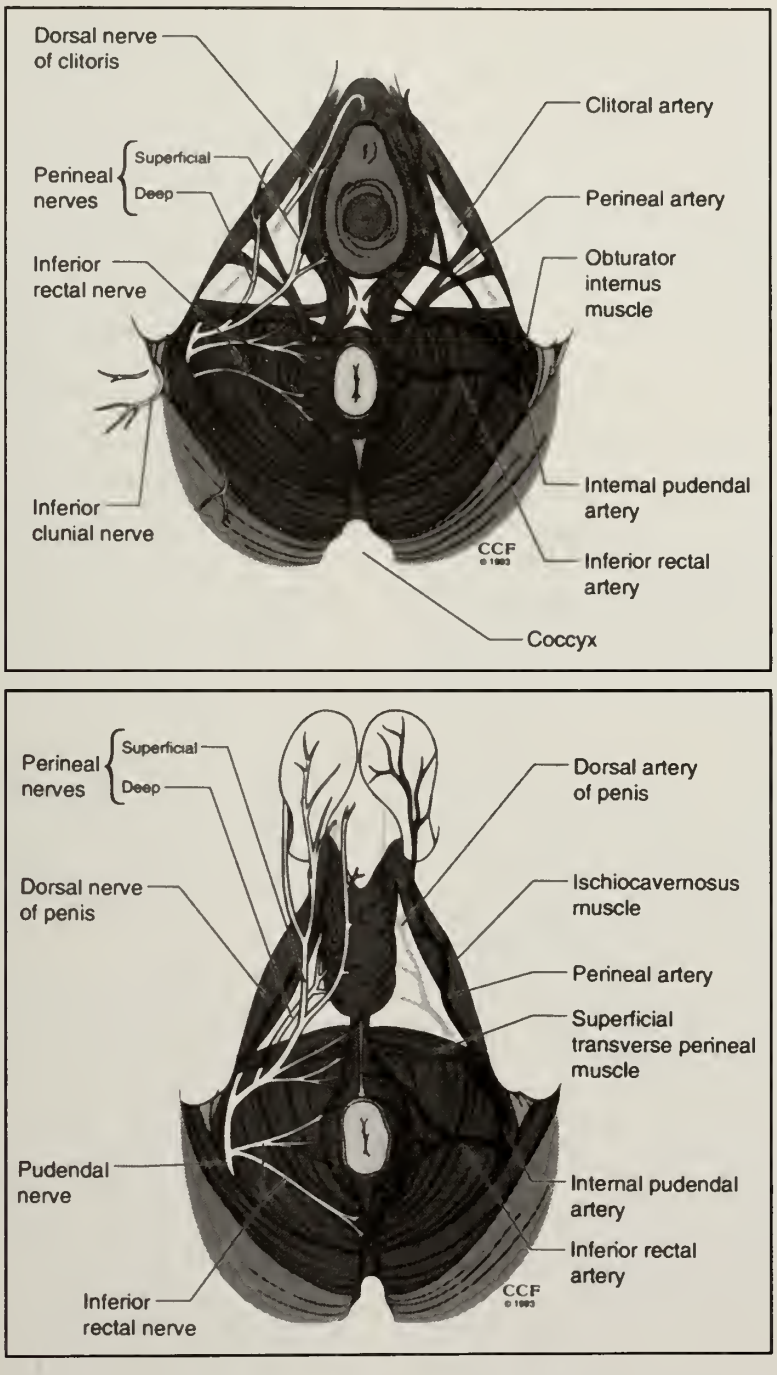

Figure 1.—Perineum superficial deep of a woman (upper panel) and a man (lower panel). Branches of the pudendal nerve are depicted on the left (white), and the pudendal artery and its branches are depicted on the right. Reprinted, with permission, from *Surgery of the Colon, Rectum, and Anus* (Mazier WP, et al., Eds; Philadelphia: Saunders, 1995, p 31).

the midportion of the anal canal and inserts posteriorly at the anococcygeal ligament and coccyx. The subcutaneous loop encircles the most distal anal canal and inserts anteriorly at the perianal skin.[9] Some experts believe that the external sphincter cannot be divided into three different loops and represents a single homologous muscle[10,11] or a dual system with a superficial and deep component only.[12] The external anal sphincter is composed of striated skeletal muscle and is innervated by the pudendal nerve (S2–S4).[4] The inferior rectal branch of

ABBREVIATIONS USED IN TEXT
EMG = electromyography
PNTML = pudendal nerve terminal motor latency

the pudendal nerve supplies the external sphincter, and afferent branches of the nerve transmit sensory impulses from the anal canal, perianal skin, and genitalia. Thus, the external anal sphincter and puborectalis muscle act as a functional, indivisible unit despite differences in their innervation.

Continence

Pelvic Floor Physiology

Continence is defined as the ability to defer defecation or passage of flatus until a socially acceptable time and place. Control of continence is multifactorial and, despite intense study, is still not completely understood. The components of the continence mechanism include the internal and external anal sphincters (the anal canal high-pressure zone), the pelvic floor musculature, the rectum, and interrelated motor and sensory neural pathways. Other factors affecting continence include colonic motility, stool volume, and stool consistency. Additionally, although in debate, a flap valve mechanism created by the puborectalis muscle and sacral attachments close off the rectum at the anorectal angle. This angulation keeps the valve closed at rest.

Pressure generated by the internal and external anal sphincters is critical to the maintenance of continence. The internal anal sphincter contributes approximately 85% of the resting tone of the anal canal, and the external sphincter and anal cushions (hemorrhoids), the remaining 15%.[13–15] The external sphincter, pelvic floor muscles, and cricopharyngeus are unique among skeletal muscles in being able to maintain a state of tonic contraction.[16] This tone is maintained by a low sacral reflex. Resting pressures are distributed unevenly around the circumference of the anal canal, but the mean anal canal resting pressure is approximately 40–80 mmHg. Tonic activity of the external anal sphincter increases with factors that increase intraabdominal pressure such as erect posture, coughing, or Valsalva maneuver.[3] Voluntary contraction of the external anal sphincter is normally able to approximately double the resting pressure in the anal canal.[17] The external sphincter fatigues after 3 minutes of sustained voluntary contraction.[18]

Distension of the rectum with gas or stool stimulates receptors located in the pelvic floor, causing a reflex receptive relaxation of the internal anal sphincter. This reflex is known as the rectoanal inhibitory reflex. It has been shown to occur up to seven times a day.[20] Relaxation of the internal anal sphincter lowers anal canal pressure, allowing rectal contents to come in contact with the mucosa of the upper anal canal in the anal transition zone. The mucosa of the anal transition zone is richly innervated with both free and organized nerve endings that are able to discriminate the nature of the rectal contents.[21] Simultaneous with the rectoanal inhibitory reflex, a reflex contraction of the external anal sphincter, known as the rectoanal contractile reflex, prevents inadvertent loss of stool or gas.[22] Progressive distension of the rectum causes continuous inhibition of the internal sphincter and relaxation of the external sphincter causing an urge to defecate.[18]

The puborectalis muscle is contracted in the resting state, maintaining an anterior pull on the intestine, resulting in an acute angulation of the junction of the rectum and anal canal known as the anorectal angle. It is radiographically defined as the angle formed by a line drawn along the posterior wall of the anal canal and a line drawn along the distal posterior wall of the rectum. Squeezing the anal sphincters causes the anorectal angle to become more acute, while sitting and squatting leads to a more obtuse anorectal angle.[23] The anorectal angle has been proposed to play an important role in the maintenance of continence but the exact mechanism is disputed.[24,25]

The normal rectum is a capacitance organ and plays an important role in the maintenance of continence. The rectum accommodates passively to increases in volume while maintaining a low intraluminal pressure. Capacitance allows defecation to be deferred during continual rectal filling. While rectal filling is appreciated with a volume of as little as 10 ml, the rectum can tolerate a volume of up to 300 ml until a sense of fullness and an urge to defecate develops. The volume required to elicit a sensation of urgency varies from patient to patient and likely represents a learned response.

Neural pathways involved in the control of continence are incompletely understood. They include local nerve plexuses in the wall of the rectum, sensory receptors in the pelvic floor and the lining of the anal canal, regional spinal reflexes, and ultimately higher control centers in the brain for deferring defecation until socially acceptable conditions permit.

There are a number of factors that, although not important in the maintenance of continence, can significantly affect continence. These include such factors as stool volume, stool consistency, and colonic motility. The capacity of a normal rectum may be overwhelmed by excessively rapid filling due to excessively fast colonic transit. Incontinence can result in the presence of an otherwise normal continence mechanism in the presence of, and excessive volume of, liquid stool.

Defecation

Normal defecation occurs when peristalsis propels a fecal bolus from the sigmoid colon into the rectum. Distension of the rectum initiates the rectoanal inhibitory reflex causing relaxation of the internal anal sphincter, allowing the rectal contents to come in contact with the sensory receptor–rich anal transition zone, which in turn allows discrimination between solid stool, liquid stool, and gas (sampling reflex). At the same time, the rectoanal excitatory reflex contracts the external anal

sphincter, preventing loss of stool. The integrated neural pathways activate higher cortical centers, and a determination is made about whether it is a socially acceptable time and place to defecate. If it is, the person assumes a sitting position on the toilet which straightens the anorectal angle. Straining is associated with a reflex relaxation of the puborectalis muscle and external anal sphincter. This allows descent of the pelvic floor, further straightening the anorectal angle. Thus, the anal canal shortens and becomes more funnel-shaped as it begins to open. Rectal evacuation is then primarily accomplished by increasing intraabdominal pressure due to contraction of the abdominal muscles, the diaphragm, and performance of a Valsalva maneuver. After complete evacuation, sphincter pressures return to normal, the puborectalis muscle returns to its normal state, and the anorectal junction resumes its normal acute angulation. Although lacking normal sensation, patients with spinal cord injuries are able to initiate the reflex mechanisms involved in normal defecation by digital stimulation, and thus initiate a bowel movement through the integrated neural pathways mentioned above.

Investigative Tools

Patients can present with a variety of complaints referable to abnormal pelvic floor function. In addition to a accurate history and physical examination, there are a number of objective tests available to evaluate the complaints and come to an appropriate diagnosis.

Anorectal Manometry

Anorectal manometry measures intraluminal pressures generated by the internal and external anal sphincters. Use of a thin, flexible, hydraulically perfused polyvinyl catheter with radially located channels is the most common method. The catheter is connected to a pressure transducer which is linked to a polygraph to provide a continuous tracing. The examination is typically performed in the left lateral decubitus position. The catheter is inserted approximately 8 cm into the anal canal, and the rectal pressure is recorded. The catheter is then slowly withdrawn until a rise is noted. This is the beginning of the anal canal high pressure zone. The distance from the anal verge is recorded, allowing determination of the length of the anal canal. The maximum resting pressure is the maximum pressure generated in the anal canal with the patient at rest. The internal anal sphincter is responsible for 80–85% of the resting tone, with the remainder due to tonic action of the external anal sphincter. Maximum voluntary contraction is determined by asking the patient to squeeze and represents action of the external anal sphincter. In patients who are unable to squeeze in a laboratory setting, the pressure generated during a cough usually accurately reflects squeeze pressure. The presence of the rectoanal inhibitory reflex is determined by inflating a balloon in the rectum while simultaneously measuring intraluminal pressure in the anal canal. The expected response is a decrease in the resting tone of at least 50%.

Absolute manometric values overlap considerably between "normal" patients and those with disorders of defecation. The values are useful, however, when taken in the clinical context. They are also useful in predicting and measuring responses to therapy.

Rectal Sensation

Rectal sensation can be determined by inflating an intrarectal balloon with increasing amounts of air. The balloon is serially distended with 10-ml volumes of air. The initial sensation is usually felt at about 20 ml. Recorded values include volume necessary to cause first sensation, volume necessary to cause urge to defecate, and maximum tolerable volume.[26] Rectal compliance can be measured by measuring the pressure in the distending balloon.

Abnormalities of rectal sensation are seen in both constipated and incontinent patients. Patients may have severe constipation and lack the urge to defecate due to an inability to sense stool in the rectal vault. Conversely, other patients with abnormal rectal sensation present with incontinence secondary to inability to sense stool in the rectum.

Defecography

Rectal evacuation requires coordinated activity or inactivity of the abdominal muscles, internal anal sphincter, external anal sphincter, and pelvic floor. The dynamics of defecation can be assessed radiographically using cinedefecography.[27] The patient is placed on a radiolucent commode and the rectum filled with a thick barium paste. The patient is then asked to squeeze, cough, strain, and then empty the rectum while lateral fluoroscopic views of the pelvis are obtained. Static images are useful for determining length of the anal canal; the anorectal angle at rest, during squeezing, and during evacuation; and degree of perineal descent.

Defecography qualitatively assesses puborectalis function and adequacy of rectal emptying. It also permits real-time visualization of rectocele, enterocele, and internal rectal intussusception. A paradoxical contraction of the puborectalis muscle, leading to obstructive defecation, is identified as *anismus*.

Electromyography

Electromyography (EMG) of the external anal sphincter and pelvic floor can be performed using either needle or surface electrodes.[28] Needle EMG can be either concentric needle EMG or single-fiber EMG. Concentric needle EMG records the summed electrical activity of approximately thirty motor units. It has been used primarily to map sphincter defects, such as after obstetrical injury. Single-fiber EMG uses a fine, 25-μm electrode. It is able to record the action potential from a single muscle fiber and is able to quantify fiber density. An increase in fiber density occurs with denervation due to sprouting from neighboring nerve fibers. Single-fiber

EMG can also be used to measure neuromuscular "jitter," which is an electromyographic indication of denervation and reinnervation.[29] EMG has the disadvantage of being uncomfortable for the patients, and it requires considerable technical expertise on the part of the examiner.

Ultrasound has largely replaced EMG for the mapping of sphincter defects, although EMG is still useful in the diagnosis of neurogenic fecal incontinence and in the demonstration of the abnormal recruitment of muscle fibers in anismus or the nonrelaxing puborectalis syndrome.

Pudendal Nerve Terminal Motor Latency

Pudendal neuropathy plays a role in the pathogenesis of idiopathic fecal incontinence. It is possible to diagnose injury to the pudendal nerve by measuring nerve conduction velocity. This is accomplished by digital rectal examination using a special glove-mounted electrode. The ischial spine is palpated, and the pudendal nerve is stimulated in Alcock's canal. The evoked electrical response in the external anal sphincter is recorded in an electrode at the base of the finger. The time from the stimulus of the pudendal nerve at the ischial spine to the recording of electrical activity of the external anal sphincter represents the pudendal nerve terminal motor latency (PNTML). The normal PNTML is 1.9 ± 0.2 seconds.[30] Any nerve injury will give a prolonged PNTML.

Measurement of PNTML is primarily used to diagnose pudendal neuropathy and neurogenic fecal incontinence. It is useful in predicting which patients will benefit from biofeedback and surgical intervention.

Ultrasonography

An ultrasound examination of the anal canal using a rigid, rotating 7.5 or 10.0 MHz transducer is able to define accurately the anatomy of the anal canal. It is able to measure the thickness of and define defects in the internal anal sphincter. It is also able to identify defects in the external anal sphincter and is much more comfortable than EMG.[31]

Ultrasound has broad applications in the diagnosis of many anorectal conditions. Incontinent patients, especially those who have had prior anorectal surgery or those in whom an obstetric injury is suspected, should have an ultrasound to rule out a sphincter defect that may be amenable to surgical correction.

Pelvic Floor Dysfunction

Neurogenic Incontinence

Fecal incontinence is defined as the inability to defer defecation to an appropriate time or place. It has been shown to occur in more than 2% of the general population. Many people are reluctant to admit the problem because of embarrassment, and thus the true incidence may be higher.[32] Fecal incontinence can be classified as traumatic (obstetric injury, anorectal surgery), neurologic, congenital, or idiopathic. Idiopathic fecal incontinence is generally believed to be due to denervation of the pelvic floor and external anal sphincter due to stretch injury to the pudendal nerve.

It is theorized that the terminal portion of the pudendal nerve is susceptible to stretch injury due to descent of the pelvic floor. This is seen in conditions such as chronic straining, descending perineum syndrome, intussusception, or prolapse, or after difficult vaginal delivery. Stretch injury to a peripheral nerve occurs when it is stretched more than 12% beyond its original length. It has been calculated that the terminal portion of the pudendal nerve is stretched 20–30% with an average descent of only 2 to 3 cm (normal descent up to 4 cm).[31] The fast conducting myelinated fibers of the pudendal nerve are those susceptible to stretch injury. Some stretch injury is reversible, but the degree or amount of stretch necessary to cause irreversible damage is not known.

A study of the effect of vaginal deliveries on pelvic floor musculature found that 80% of primagravida sustained reversible pudendal nerve damage.[33] Nerve injury may be unilateral or bilateral.[30] The end result is a denervation and weakening of the pelvic floor and external anal sphincter. As the pelvic floor weakens, it is less able to withstand increased intraabdominal pressure, resulting in further perineal descent. The neuropathy and sphincter dysfunction progress with time.[34]

The descending perineum syndrome is a relatively common disorder, primarily in women. The most pronounced feature is difficulty with defecation with repeated efforts of unsuccessful straining and a sense of incomplete evacuation. Straining leads to descent of the pelvic floor and straightening of the anorectal angle. This leads to prolapse of the anterior rectal wall into the rectal lumen which can obstruct defecation, setting up a vicious cycle with further straining. The end result is often further pelvic descent, stretching of the pudendal nerve, denervation of the pelvic floor and external anal sphincter, and finally, neurogenic fecal incontinence, sometimes accompanied by internal rectal prolapse (intussusception).[54]

Although stretch injury to the pudendal nerve is a common cause of neurogenic fecal incontinence, any neurologic disease may affect bowel control. Diabetes is a common condition that may cause diarrhea or produce a peripheral neuropathy, both of which may lead to incontinence.

Fecal incontinence is an underdiagnosed condition because patients are reluctant to discuss it with their physicians. Except in the most minor cases, patients with fecal incontinence should be referred to a colorectal surgeon or gastroenterologist for full evaluation. The diagnosis of incontinence due to pudendal nerve injury begins with a careful history detailing the patient's bowel habits, generalized pelvic floor function, and obstetrical history (Figure 2). In particular, the character (gas, liquid, or solid stool) and frequency of the incontinent episodes must be elicited, as well as a preceding history of chronic straining at stool. Associated uterine prolapse or stress urinary incontinence suggests generalized pelvic floor

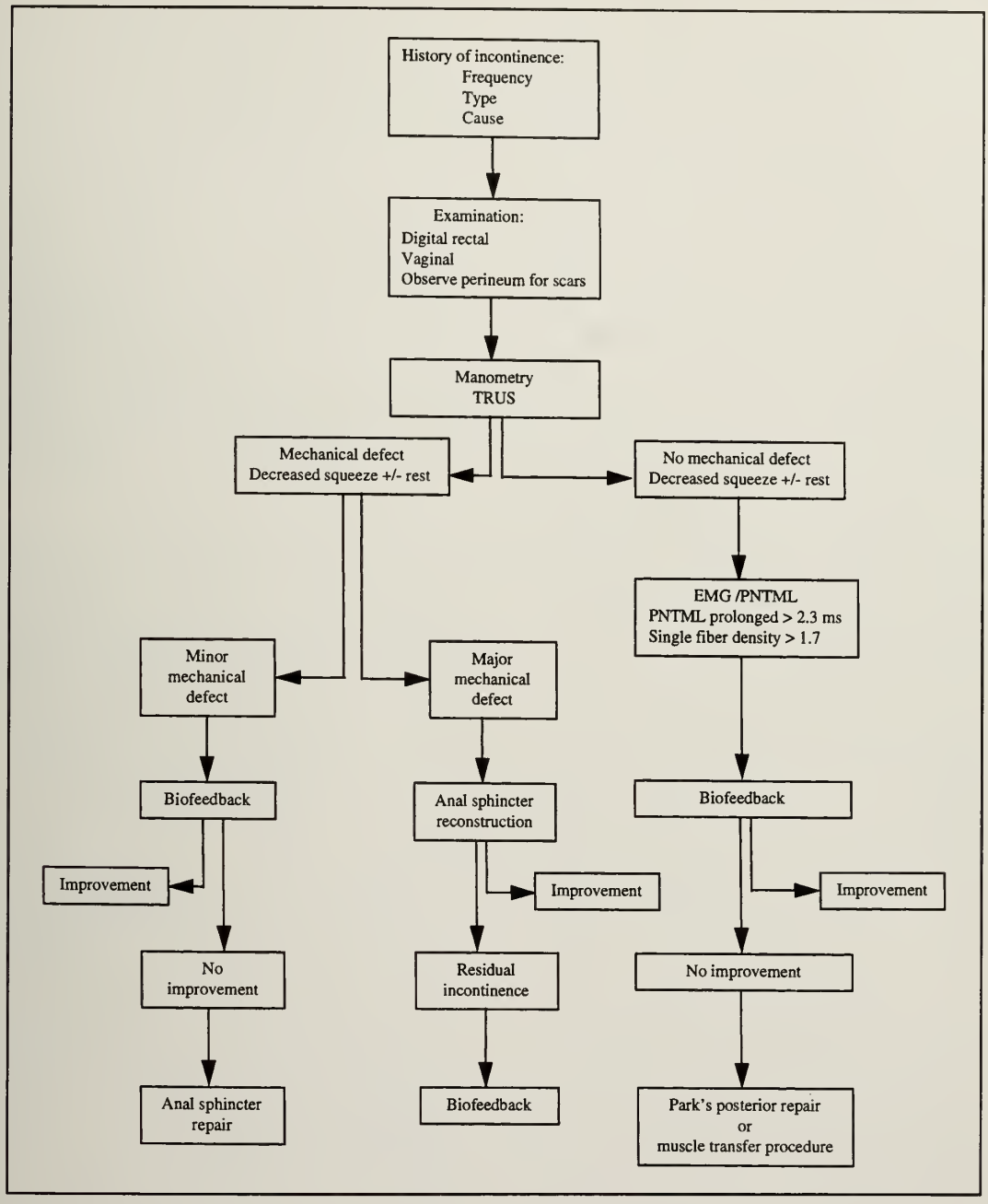

Figure 2.—Algorithm for work-up and treatment of fecal incontinence.

weakness. Finally, history of a prolonged and difficult second stage of labor, forceps delivery, or high birthweight also suggests nerve injury. Physical examination typically reveals a patulous anus and flattening of the perineum. Straining generally causes abnormal perineal descent. There may be altered perianal sensation and absence of the anocutaneous reflex. Digital rectal examination reveals weakened resting tone and decreased ability to augment pressure with squeeze. Manometry may be normal or reveal decreased resting and squeeze pressures.[35] Defecography may show a widened (more obtuse) anorectal angle and abnormal perineal descent on straining. However, the diagnosis of incontinence due to pudendal neuropathy rests on showing prolonged pudendal nerve terminal motor latency or evidence of denervation and reinnervation on EMG. A PNTML of greater than 2.2 seconds indicates pudendal nerve injury. This can be confirmed by finding a single fiber density greater than 1.66 using single-fiber EMG.[36] Ultrasonography may reveal an unsuspected sphincter defect.[28]

Management of patients with neurogenic fecal incontinence due to pudendal neuropathy often begins with

long trials of conservative medical measures. Changing stool consistency from liquid to solid may significantly decrease the number of incontinent episodes in patients with marginal sphincter function. Lomotil, loperamide, and codeine achieve this change in stool consistency by delaying colonic transit allowing increased absorption of water. Bulking agents such as psyllium bind water and thicken the stool. Immodium also tends to increase the resting tone of the anus.

Biofeedback is a technique that translates a physiologic function into an auditory or visual stimulus, thus allowing the patient to learn to control the physiologic function. During training, intraanal pressure or external sphincter myoelectric activity is transformed into an acoustic or visual signal which is fed back to the patient. The patient uses these signals to develop improved control of the sphincter function. Sensory function may also be improved by inflating a balloon in the rectum and training the patient to detect decreasing volumes in coordination with contraction of the external sphincter. Studies have shown a reduction of incontinent episodes in up to two-thirds of patients,[17] but objective improvement, such as increase in resting or squeeze pressure, is lacking.[37]

For patients with more severe neurogenic incontinence, or those who have failed nonoperative measures, there are several surgical options available, some of which are still experimental. One option is the postanal repair. The posterior aspect of the external sphincter, puborectalis, and levator ani are plicated in an attempt to restore the normal anorectal angle and lengthen the anal canal.[38] Although improvement was shown in 80% of patients in early studies, more recent studies have been less promising. Therefore, this operation is rarely performed in the US today.[39,40] Postanal repair generally is a reefing of external sphincter and does not involve an anterior approach, which may be confined to reef the external sphincter anteriorly and plicate the puborectal anterior. This aids in increasing passive resistance and active contraction. This repair may also be of benefit in restoring normal anal distance from the vagina when the anus is ectopically displaced anteriorly. The remaining restorative options attempt to create a controllable anal sphincter. A neosphincter using skeletal muscles based on its own neurovascular pedicle is one such option. Muscle, either the gracilis or gluteus maximus, is mobilized and wrapped snugly around the anus, and the tendon is sutured to the contralateral ischial tuberosity. Chronic electrical stimulation of the muscle graft with an implantable pulse generator converts the muscle fibers from fatigable, fast-twitch to fatigue-resistant slow-twitch muscle fibers that are capable of maintaining the prolonged contractions necessary for continence. Although this is a technically difficult operation, results using this technique have been promising.[41] An experimental, implantable, artificial anal sphincter composed of three silastic components (an inflatable cuff, a pressure-regulating balloon, and a control pump) has been developed. The inflatable cuff is implanted around the anus and is connected to the control pump situated in the scrotum or labia. The control pump is connected to the pressure-regulating balloon and is placed in the preperitoneal space behind the pubic bone. In its activated state, the cuff is inflated with fluid, the anus is occluded, and continence is maintained. When the patient experiences an urge to defecate, the cuff is deflated by pumping the control pump. In two recent studies, a successful outcome was achieved in 75–90% of patients.[42,43] Implantable neuroprostheses to directly stimulate the sacral nerve roots, pudendal nerve, or external sphincter itself to achieve continence are techniques currently under investigation. Sacral nerve root stimulation has shown promise in the treatment of urinary incontinence.[44] A diverting colostomy is the final surgical option for patients with ongoing significant incontinence despite medical treatment, biofeedback, or surgical intervention.

Nonrelaxing Puborectalis Syndrome

As discussed previously, normal defecation requires a series of coordinated actions of the pelvic floor and sphincter muscles. Obstructed defecation is a form of chronic functional constipation due to functional abnormalities of the pelvic floor and anal canal musculature leading to pelvic outlet obstruction. Obstructed defecation may be due to a variety of causes including rectocele, rectal prolapse, and aganglionosis of the anorectal junction (adult Hirschprung's disease). The most common cause, however, is anismus, or the nonrelaxing puborectalis syndrome.[45–48] The cause of the syndrome is unknown, but the main physiological abnormality is thought to be due to failure of the pelvic floor muscles to relax during defecation. This prevents straightening of the anorectal angle.[49] Thus, the patient strains against an acute anorectal angle which obstructs normal defecation. Anismus is thought to be an abnormal learned response. In some patients, it represents a reaction to sexual assault. Ironically, the end result of long-term anismus is often neurogenic incontinence as a consequence of chronic straining with resultant perineal descent and resultant stretch injury to the pudendal nerve.

Constipation is a very common condition, and most patients with a complaint of infrequent or difficult bowel movements do not require extensive work-up. A thorough history will often uncover a change in diet, medication or physical activity that is easily corrected. The physical examination should include a complete visual, digital, anoscopic, and sigmoidoscopic evaluation to rule out common and potentially serious causes of constipation such as anal stenosis, anal fissure, distal colorectal malignancies, extrinsic pelvic massess, and ischemic or inflammatory strictures of the rectosigmoid. When these causes of constipation are ruled out, conservative management consists of a high-fiber diet and increased fluid intake. If this fails, referral to rule out colonic inertia or anismus is indicated. Patients with anismus typically present with complaints of months to years of difficult evacuation with many unsuccessful calls to stool (Figure 3). They often spend minutes to

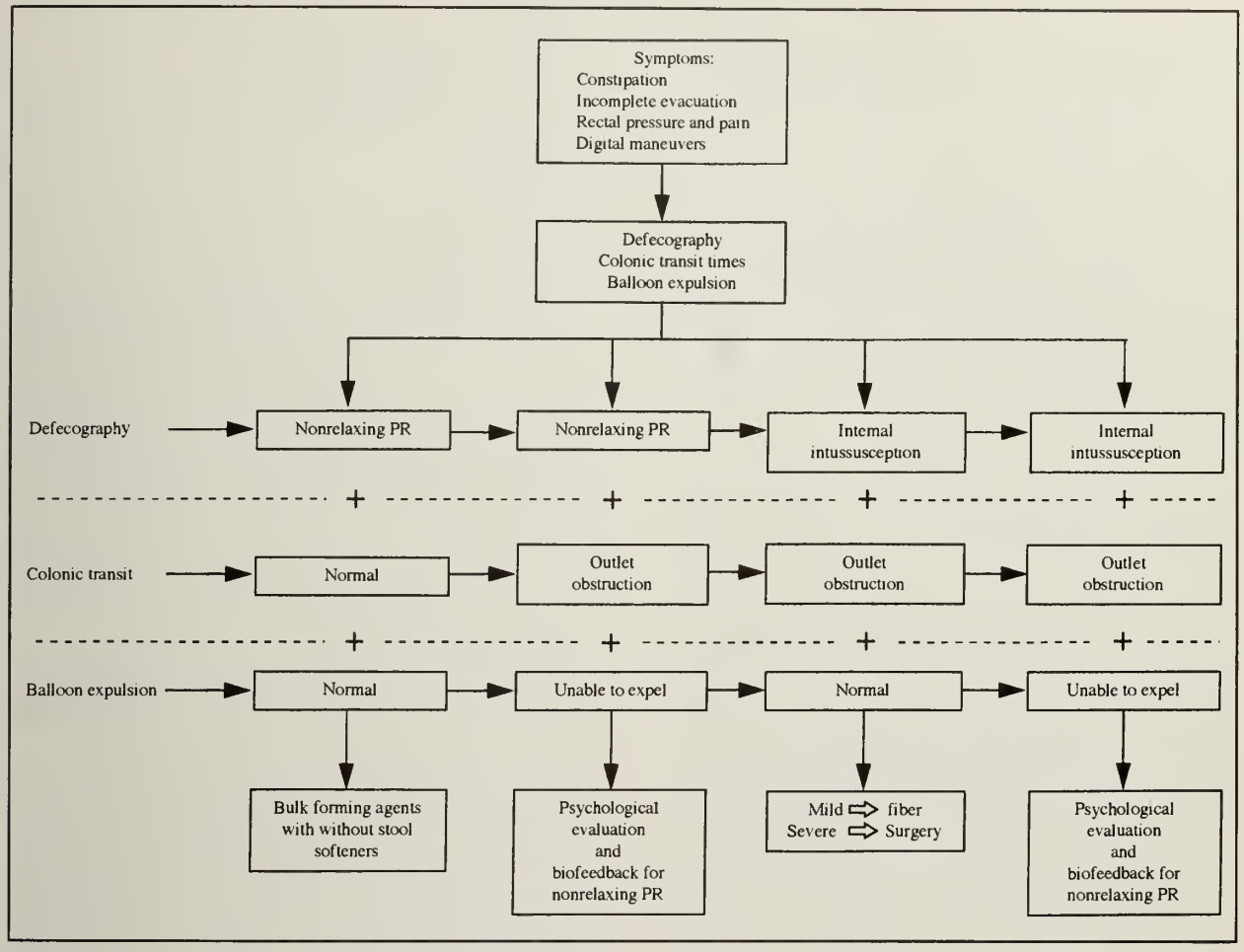

Figure 3.—Algorithm for work-up and treatment of obstructed defecation.

hours on the toilet without results. They complain of an inability to initiate defecation, a sense of incomplete evacuation, and pelvic or perianal pain. Physical examination is often normal, but may reveal abnormal perineal descent or a persistent, palpable puborectalis muscle posteriorly on straining. There is no consistent characteristic abnormality of the internal or external sphincters on anorectal manometry.[50] Defecography and EMG demonstrate absence of relaxation, or paradoxical contraction, of the puborectalis muscle during attempts to defecate. Defecography may also reveal a poorly emptying rectocele or internal intussusception, both of which lead to a sense of obstructed defecation. Needle electromyography of the pelvic floor can be painful, but surface electromyography using an anal plug can also demonstrate increased activity in the puborectalis muscle and external sphincter during straining to defecate. A useful comfirmatory test for the diagnosis of anismus or nonrelaxing puborectalis is the ability to expel an air-filled 60-ml balloon catheter. Failure of the patient to expel the balloon is highly suggestive of anismus.

Early surgical attempts to treat anismus by partial division of the puborectalis muscle have proven unsatisfactory.[51] Partial paralysis of the puborectalis muscle by injection of botulinum toxin has also proven unsuccessful.[52] Treatment, therefore, is primarily nonoperative. Patients are placed on a high-fiber diet coupled with adequate hydration. Patients with documented nonrelaxing puborectalis demonstrated by either defecography or balloon expulsion test should be offered biofeedback. Using the same biofeedback techniques described for the management of incontinence, the patient is taught to strain without contracting the puborectalis muscle. In our experience in patients without other ongoing psychological issues, biofeedback has been 80% effective in treating anismus, while others have reported that up to 90% of the patients improve.[53]

Conclusions

The normal coordinated actions of the pelvic floor are often taken for granted. However, functional disturbances of the pelvic floor leading to disturbances in defecation can be quite distressing. Fecal incontinence is an

embarrassing condition that often leads to self-imposed social isolation and is a major health care problem in that it is a leading cause for nursing home admissions. Severe constipation may lead to frustrating hours straining on the toilet, debilitating abdominal pain, and multiple visits to primary caretakers, gastroenterologists, and surgeons. These functional disorders are readily diagnosed by history and a variety of diagnostic tests available in a well-equipped anorectal physiology laboratory. Neurogenic fecal incontinence and obstructed defecation due to a nonrelaxing puborectalis are usually readily managed with medical means and biofeedback. A number of surgical options are available for the incontinent patient who fails these less invasive treatments.

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Epitomes

Important Advances in Clinical Medicine

Plastic Surgery

Robert A. Hardesty, MD, FACS, and Harvey Zarem, MD, Section Editors

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in plastic surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in plastic surgery that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Plastic Surgery of the California Medical Association, and the summaries were prepared under the direction of Drs Hardesty and Zarem and the Panel.

Advances in Microvascular Free Tissue Transfer

PERHAPS MORE THAN ANY other technique developed in the recent past, microvascular surgery has expanded the horizons of reconstructive surgery. Aided by the Western experimental background and the considerable Chinese clinical experience in microsurgery, microvascular free tissue transfer has gradually evolved from being a procedure of last resort to becoming the first choice for reconstruction. Improved success rates, shorter operative time, and reduced patient morbidity have widened the indications for the procedure, which now include oncologic patients following resection and radiation, traumatic defects and congenital defects such as moebius syndrome.

The greatest benefit of a microsurgical approach to head and neck reconstruction is improved blood supply, to both the tissue being transferred and the recipient site. The increased blood supply has improved tissue survival and wound healing under such compromised circumstances as prior radiation and infection.

Despite the slightly longer initial operating time and the special microsurgical expertise required, free flaps are important options in many patients desiring breast reconstructions. When there is not enough tissue or the tissue has been irradiated and is unable to be easily transferred from a nearby or local area, a vascularized pedicle is obtained with the artery and vein anastamosed to vessels in the affected area, bringing skin, soft tissue (e.g. muscle, omentum) and even bone to reconstruct this region. The technique can be done with a highly acceptable failure rate (1.8%) and gratifying results.

In most cases of local flap use, the wounds have been partially devitalized by resection or radiation. Flaps with marginal circulation, while they may survive, are unable to resist the effects of bacterial contamination. Salivary leaks rapidly lead to wound breakdown and orocutaneous fistulae. By contrast, well-vascularized tissue with an abundant blood supply contributes greatly to the healing potential of the repair. An important example is the ability of vascularized bone to unite after mandible reconstruction, despite both radiation and bacterial contamination.

Ischemic lesions of the legs, ankles, and feet leading to soft tissue and bony involvement are major problems, particularly in diabetic patients. Microsurgical techniques can facilitate revascularization of extremely small, badly diseased distal vessels of the leg and foot in many of these patients. The addition availability of microsurgical free tissue transfer to reconstruct major soft tissue and bony wounds in these conditions has resulted in salvage of limbs that otherwise would have been amputated.

As success at the recipient site has now become so routine, further outcome improvement has been directed toward enhancing the appearance and residual function at the donor site.

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Facial Fractures in Children

FACIAL FRACTURES ARE relatively infrequent in children. The age group from birth to 5 years accounts for only 1% of all fractures observed, and from 5 to 12 years, only 3–5%. Anatomic factors play a role—the child's face is stronger than the adult's because the sinus cavities are not yet developed; the bone structures are more pliable because the proportion of cancellous to cortical bone is higher. In newborns, the bony volume of the face with respect to the cranium is 1:8; that of adults is 1:2. Children's cranial sutures are not fused, their midface is foreshortened, with abbreviated midface buttress, and children between the ages of 6 and 12 years have mixed dentition. Furthermore, children are closely supervised up to school age, and the usual injuries associated with children occur at low velocity.

When they do occur, facial fractures in children pose special problems. Environmental, anatomic, and developmental factors involved in treating children call for thorough evaluation with liberal use of computed tomography (CT) scans, conservative treatments favoring the least invasive procedures, and close patient monitoring and follow-up.

Initial evaluation is similar to that of adults. In early management, maintenance of the child's airway can be difficult. Also, children have a high incidence of associated intracranial injury, and "small" blood loss can lead to shock. Fractures of the nose, dentoalveolar complex, and lower jaws are relatively common; fractures of the midface are rare. Of mandibular injuries, condylar fractures are especially common.

Alveolar fractures with dislodged teeth can be salvaged with adequate support by using arch bars or fixing with acrylic splints. In severe fractures of the alveolar ridge, the fragmented bones should be left in place and the soft tissue closed. Tooth extraction is common, especially in the period of mixed dentition. High Le Fort fractures (horizontal fractures of the maxilla) are rare in the pediatric population, since the high-energy trauma needed to disrupt the cartilaginous suture lines frequently results in severe brain insult and death. Fractures of the upper face are managed as in adults, but early treatment is of higher importance in children. Definitive anatomic reduction should be instituted within the first 48 hours. After 7 days, reduction of fractures becomes difficult, and after 14 days, next to impossible.

The general principles of treating mandibular fractures are the same in children and adults: the bony fragments must be reduced to their preinjured position, occlusion reestablished, and stabilization provided until healing. Treatment of children is more conservative, however. To avoid injury to the tooth buds, plate fixation is seldom pursued. Displaced fractures of the mandibular angle or body are treated by open reduction and internal fixation or splints. If noted to have minimal displacement or green stick fractures, condylar neck fractures may be treated with soft diet and observation. Condylar fractures are generally treated closed, except in the case of fracture dislocation of the condyles with open bite and interference with movement or inability to maintain reduction. Bilateral condylar fractures usually require skeletal wiring. Early motion is important at 2 to 3 weeks to avoid the development of temporomandibular joint ankylosis.

Most health care centers favor closed reduction techniques for mandibular condyle fractures and open reduction techniques for other regions of the facial skeleton. Because of concern about the effect of rigid fixation in facial growth, and since displacement and migration of plates and screws intracranially have been noted, fixation structures are often removed after healing.

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Computerized CO_2 Laser Resurfacing for Aesthetic Management

COMPUTERIZED CO_2 LASER RESURFACING of the facial skin has proven to be a valuable contribution to the field of aesthetic surgery. When used appropriately, techniques such as chemical peels and mechanical dermabrasian give excellent results, but they have limitations. A desire for greater control, decreased risk of scarring, and the ability to remove deeper wrinkles and tighten skin has opened the door for carbon dioxide laser resurfacing.

In CO_2 resurfacing, laser light is applied to the skin and is absorbed by the water in the outer cellular layers. Energy levels must be sufficient to cause instant vaporization of the targeted outer layers. In addition, the timed pulse duration must be short so that the vaporization is rapid, preventing conduction of heat from damaging surrounding tissues. CO_2 lasers have been used in plastic surgery for several decades, but only the most recent generation of machines control spot size, energy, and pulse duration by computer, minimizing thermal destruction of adjoining tissues. In addition, computerized pattern generators have allowed the laser to treat large areas rapidly.

In addition to smoothing the skin by removing excessive facial wrinkles, the thermal effect of the laser causes shrinkage of collagen fibers, which results in tighter skin. Patients with fair complexions are the most desirable candidates; African-Americans and those with olive skin are typically not good candidates. The CO_2 laser is

also effective for acne scarring, but sometimes several treatments at intervals of 6 months or so are necessary.

Pretreatment of the skin—strict sun avoidance and use of a sun block, retinoids, and hydroquinone—is essential to good result. Most patients are also pretreated with antibacterials and antiviral prophylaxis for herpes simplex virus infection. Patients who have been on Accutane are advised to wait 12–18 months before undergoing the procedure.

Laser resurfacing is performed on an outpatient basis, unless it is combined with other, larger, procedures. It can be performed with light sedation and facial sensory nerve blocks, but many patients and surgeons prefer general anesthesia. The endotracheal tube is protected with aluminum foil, metal shields are placed in the eyes, and the patient is draped with wet towels to prevent fires and injuries, fortunately a very rare occurrence.

The treatment may involve the entire face or just the "crow's feet" or perioral areas. One pass, removing the epidermis, is made over the entire area to be treated. Typically a second, and occasionally a third or fourth pass, is then done, causing ablation of varying depths of the dermis. The necrotic residue is wiped away after each pass. Care must be taken to preserve the reticular dermis, which is usually noted by its chamois color.

Facial nerve blocks, topical lidocaine, and a closed dressing (Xeroform) have rendered the postoperative course almost pain-free.

Postoperatively, most patients re-epithelialize in 4–5 days. During that time, most practitioners leave a semi-occlusive dressing on and ask their patients to soak their face with a dilute acetic acid solution. By 10–18 days after resurfacing, most patients are healed well enough to apply camouflage make-up and resume social activities. Redness is present in the initial few weeks, but the use of pulsed topical steroids and topical nonsteroidal anti-inflammatory drugs (NSAIDs) have shortened the duration and intensity of the redness.

Complications include herpesvirus, bacterial, and yeast infections, which are usually preventable or easily manageable. Hyperpigmentation is common, though usually preventable by good preoperative skin preparation, and is treatable with hydroquinones or kojic acid. Hypopigmentation is more difficult to treat, but occurs less often and may be prevented by avoiding treating patients with dark skin and controlling the depth of the treatment. Full thickness injury and scarring can occur from overly zealous treatment and, rarely, from the unpredictable individual healing characteristics of certain patients.

Patient and surgeon satisfaction with this procedure is high. Future developments will probably better define safe parameters for deeper treatments, treating patients with more darkly pigmented skin, and understanding safe margins of performing laser resurfacing at the same time as facelifts.

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Correction of Velopharyngeal Insufficiency Using the Furlow Double-Opposing Z-plasty

Velopharyngeal insufficiency (VPI) occurs in about 20% of patients with repaired cleft palate and in about 10% of those with unrepaired submucous cleft palate. When VPI occurs, it can be manifested in speech in a variety of ways, including hypernasal resonance, nasal emission, nasal substitutions, and compensatory articulation. Numerous surgical and nonsurgical methods exist for the treatment of VPI. The most common surgical procedures are pharyngeal flap and sphincter pharyngoplasty. These methods have a variety of complications, the most serious of which is airway obstruction. Nevertheless, most clinicians agree that the morbidity associated with secondary palatal management is outweighed by the benefits for speech communication, at least when VPI is severe. When VPI is minimal but speech quality is negatively affected, the decision to operate becomes more difficult.

Over the years, several procedures have been suggested for addressing cases of minimal VPI. The most frequently cited have been push-back or lengthening procedures and posterior wall augmentation. Recently, the theoretical advantages of the Furlow palatoplasty have made it an attractive method for treating some cases of VPI. Studies have shown that the Furlow Z-plasty increases palatal length at the expense of width and correctly reorients the levators and palatopharyngeus muscles, thus thickening the velum. It is particularly useful for patients with abnormal insertion of the levators, who have endoscopic or radiographic evidence of a small, central velopharyngeal gap with good velar motion.

Generally, the Furlow procedure has been suggested for velopharyngeal gaps of 5 mm or less. With increasing experience with patient selection and modification of the flap design, however, increases in length up to 10 mm have been reported. The success rate for the procedure—in carefully selected patients who had in-depth preoperative evaluations—ranges from 88% complete elimination of VPI without hyponasality or airway obstruction in patients with previously repaired clefts to 97% in patients with unrepaired symptomatic submucous clefts. Most importantly, no instances of postoperative airway obstruction have been reported.

These results suggest that the Furlow double-opposing Z-plasty is a valuable addition to the armamentarium of procedures for treating VPI. The procedure may be particularly well suited for patients with minimal VPI, in

whom the risks of airway obstruction associated with traditional secondary palatal management outweigh the potential benefits of improvements in speech.

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Alerts, Notices, and Case Reports

Development of Hepatocellular Carcinoma After Clearance of Hepatitis C Virus With Interferon Therapy

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CHRONIC HEPATITIS C VIRUS (HCV) infection is the most common cause of cirrhosis and hepatocellular carcinoma in the US.[1] Recent studies have demonstrated the presence of HCV RNA in both cancerous and noncancerous liver tissue.[2,3] Whether HCV is directly oncogenic, however, remains to be elucidated.

Interferon-α is an established antiviral therapy for chronic HCV. Eradication of HCV from blood, liver, and peripheral blood mononuclear cells, as measured by sensitive molecular biological techniques, has been reported in long-term responders to interferon treatment.[4,5] It is generally assumed that eradication of HCV by antiviral therapy halts the progression of disease and therefore also prevents the clinical complications associated with this chronic viral infection. A recent case at our institution, however, has caused us to reevaluate this assumption.

Report of a Case

In May 1988, a 50-year-old man came to our clinic for evaluation of his chronic liver disease. He had a history of intravenous drug use that included an episode of acute hepatitis with jaundice approximately 30 years previously. A liver biopsy specimen obtained 8 months before the clinic visit showed marked distortion of the cyto-architecture resulting from periportal fibrosis; a moderate number of proliferating bile ductules; dense lymphocyte infiltration with erosion of the limiting plates; and thin fibrous septae surrounding small nodules of normal-appearing hepatocytes. The histologic diagnosis was chronic active hepatitis with postnecrotic cirrhosis. The patient's chief complaint was fatigue, and physical examination revealed hepatosplenomegaly. Laboratory tests performed at the time of his clinic visit showed that his alanine aminotransferase count was 295 U/l, his aspartate aminotransferase 424 U/l, albumin 3.6 mg/dl, alkaline phosphatase 77 U/l, and bilirubin 0.5 mg/dl, with a prothrombin time of 14.3 seconds (control 12.5 seconds). The patient's HBsAg, HBeAg, and anti-HBe were negative, his anti-HBc and anti-HBs positive, and his serum negative for hepatitis B virus (HBV) DNA.[6] He tested negative for hepatitis A virus (HAV) and nuclear antibody. In addition, his serum ceruloplasmin level, alpha-L-antitrypsin, ferritin, serum iron, and iron saturation were all normal. His initial serum sample proved to be positive for anti-HCV by multiple-antigen enzyme-linked immunosorbent assay (Chiron, Emeryville, CA), his HCV RNA tested positive on reverse transcriptase–polymerase chain reaction (RT-PCR) analysis,[6] and his HCV genotype was 1b.

Beginning in May 1991, interferon α-2b was administered at 3 million units three times a week for a period of 2 years, after which a sustained and complete normalization of serum alanine aminotransferase was achieved. Serum HCV RNA remained consistently negative. Liver ultrasonography findings and serum α-fetoprotein levels were normal from 1988 until April 1995. In October 1995, approximately 2 years after cessation of interferon α-2b therapy, the patient's α-fetoprotein level became elevated for the first time, to 56 ng/ml; in addition, liver ultrasonography and computerized tomography (CT) scanning both showed a 3.5-cm lesion in the lateral segment of the left lobe of the liver. The patient underwent a left-lateral segmentectomy and recovered from the surgery. Microscopic examination of the noncancerous liver tissue showed the presence of numerous nodules of hepatocytes surrounded by fibrous septae. There was minimal portal lymphocyte infiltration, and a broad band of connective tissue separated the cirrhotic nodules from a trabecular type of hepatocellular carcinoma.

Serum samples from before and after interferon treatment and approximately 50 mg of fresh cancerous and noncancerous liver tissue obtained immediately after surgical removal were processed for measurement of HCV RNA by RT-PCR, as previously described.[6,7] Identical tissue samples aseptically cut into small pieces were frozen at –70°C and similarly processed at three other time intervals to check the reproducibility of the procedure. Serum extraction and RT-PCR phases were performed simultaneously with a set of both negative and positive serum controls. The negative control serum was obtained from a healthy person whose anti-HCV antibody test was negative, and the positive control serum from a patient with chronic hepatitis C who repeatedly tested positive for HCV RNA by RT-PCR. The negative liver tissue control sample was obtained from an anti-HCV antibody–negative patient, and the positive control sample from an anti-HCV–positive and serum HCV RNA–positive patient with chronic hepatitis C. Both control tissue samples were frozen at –70°C before use. As seen in Figure 1, the control serum and liver tissue from the anti-HCV–negative patient tested negative for HCV RNA by PCR (lanes 2 and 6), where-

(Tong MJ, Lai LP, Murakami-Mori K. Development of hepatocellular carcinoma after clearance of hepatitis C virus with interferon therapy. West J Med 1997 August; 167:103–105)

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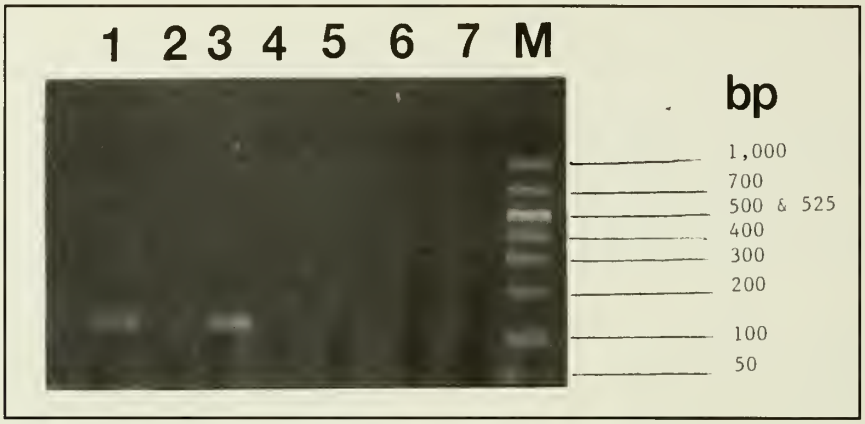

Figure 1.—Detection of HCV RNA by RT-PCR in serum and liver tissue samples obtained from patient. Lane 1 = positive serum control; lane 2 = negative serum control; lane 3 = serum before interferon treatment; lane 4 = serum after interferon treatment; lane 5 = positive liver tissue control; lane 6 = negative liver tissue control; lane 7 = noncancerous liver tissue; lane 8 = cancerous liver tissue; M = marker; bp = base pairs.

as the anti-HCV–positive control serum and liver tissue from the patient with chronic hepatitis C tested positive for HCV RNA (lanes 1 and 5). Furthermore, the patient's pre–interferon treatment serum sample was positive for HCV RNA but became persistently negative after cessation of therapy (lanes 3 and 4). Repeated RT-PCR tests for HCV RNA of cancerous and noncancerous liver tissue obtained in this patient during surgery were consistently negative (lanes 7 and 8).

In addition, approximately 50 mg of frozen cancerous and noncancerous liver tissue was tested for the presence of hepatitis B virus DNA. Each tissue sample was homogenized in DNAzol reagent (Molecular Research Center, Cincinnati, OH), and the hepatitis B virus DNA was amplified by a nested PCR procedure, as previously described.[6] For the positive tissue control, we used a frozen sample of liver tissue obtained from an HBsAg- and HBeAg-positive patient. The negative liver tissue control was obtained from a person who tested negative for HBsAg, hepatitis B core antibody, and hepatitis B surface antibody. The positive control serum was obtained from a patient whose HBsAg and HBeAg tests were positive, and the negative serum control from a person who tested negative for HBsAg and hepatitis B core and hepatitis B surface antibodies. As seen in Figure 2, the control serum and the control liver tissue were negative for HBV DNA (lanes 4 and 2), whereas the HBsAg-positive control serum and liver tissue were both positive for HBV DNA (lanes 3 and 1). The patient's cancerous and noncancerous liver tissue as well as his serum were negative for HBV DNA (lanes 5, 6, and 7).

Discussion

Chronic HCV infection is the most common cause of cirrhosis and hepatocellular carcinoma in many coun-

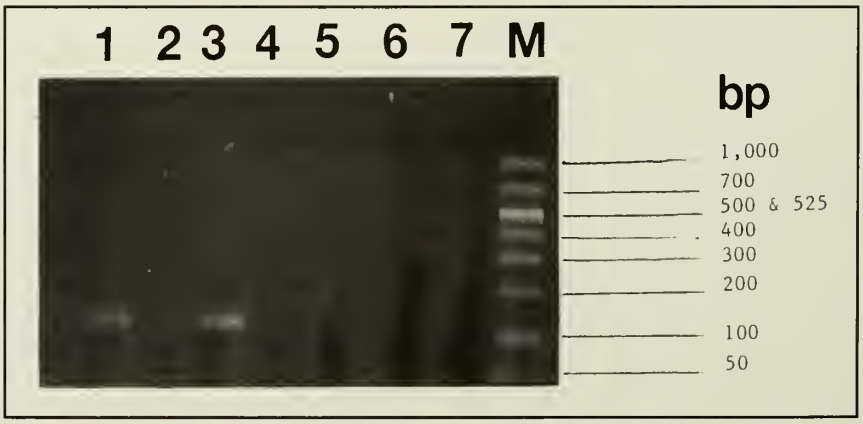

Figure 2.—Detection of HBV DNA by RT-PCR in serum and liver tissue samples. Lane 1 = positive liver tissue control; lane 2 = negative liver tissue control; lane 3 = positive serum control; lane 4 = negative serum control; lane 5 = cancerous liver tissue; lane 6 = noncancerous liver tissue; lane 7 = serum; M = marker; bp = base pairs.

tries.[1] In our recent report on hepatocellular carcinoma in patients positive for anti-HCV, we observed that 92% of cases occurred in association with cirrhosis.[8] The mechanisms of hepatocarcinogenesis in patients with chronic hepatitis C are unknown, and unlike HBV, HCV is not integrated into the genome of the human host. In addition, HCV has not been shown to activate specific oncogenes or inactivate tumor suppressor genes.[9] Chronic HCV infection is an independent risk factor for hepatocellular carcinoma in that it induces cirrhosis. It may also cause hepatocellular carcinoma in patients with already established cirrhosis.[10,11] Thus, it may have been the stimulus to liver regeneration that predisposed our patient to the eventual appearance of his tumor. This may also be the case in primary liver cancers that arise in patients with alcoholic liver disease.

In our patient, elimination of HCV after interferon therapy did not prevent the eventual development of hepatocellular carcinoma. This finding is similar to that of a recent report on a 60-year-old man with chronic HCV and cirrhosis who was successfully treated with lymphoblastoid interferon-α; in this patient, as well, a small hepatocellular carcinoma developed 1 year after cessation of treatment.[12] Our patient's medical history included a bout of acute hepatitis 30 years earlier, although it is not known whether the episode represented acute hepatitis B or C. Hepatitis B serologies in this HBsAg-negative patient were positive for both anti-HBs and anti-HBcs, indicating that he was immune to HBV. Furthermore, a "latent" hepatitis B infection was not likely, since his serum was negative for HBsAg, HBeAg, and anti-HBe, as well as for HBV DNA. In addition, the nontumor cirrhotic tissue and the hepatocellular carcinoma tissue obtained in our patient during hepatic resection in 1995 were both negative for HBV DNA. These findings are in accordance with a previous report in which it was found that HBV DNA was negative in both the serum and liver of HBsAg-negative patients with chronic hepatitis who were positive for both anti-HCV and hepatitis B antibodies.[13]

Two recent studies have indicated an association between treatment of chronic HCV infection with interferon and a decreased incidence of hepatocellular carcinoma in those patients who responded to treatment. In one randomized trial in Japan, 4% of HCV patients with cirrhosis who were treated with interferon developed hepatocellular carcinoma during a mean follow-up period of 4.4 years, compared with 38% of untreated controls.[14] In the two patients treated with interferon who developed hepatocellular carcinoma, therapy was considered ineffective because of persistently elevated alanine aminotransferase levels and positive HCV RNA tests. In another study, 3% of HCV patients with cirrhosis who were treated with interferon therapy developed hepatocellular carcinoma during a mean follow-up period of 4.1 years, compared with 10% of untreated patients.[15] In the latter study, hepatocellular carcinoma developed only in patients who did not respond to interferon treatment. These findings imply that clearance of HCV after interferon therapy significantly reduces the probability that hepatocellular carcinoma will occur. The present case, however, indicates the contrary: in our patient, hepatocellular carcinoma occurred even though HCV RNA was successfully cleared from both serum and liver after treatment with interferon. Thus, in some patients with chronic HCV and cirrhosis, elimination of HCV from serum and liver may not prevent the eventual development of hepatocellular carcinoma. Therefore, continual screening for this malignancy by α-fetoprotein testing and liver ultrasonography is necessary in all patients with HCV and cirrhosis.

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Betaxolol and Drug-Induced Lupus Complicated by Pericarditis and Large Pericardial Effusion

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DRUG-INDUCED LUPUS (DIL) is a syndrome that clinically resembles systemic lupus erythematosus (SLE) but differs in that its cause is an inciting chemical agent. Since the first report of DIL in 1945, a case induced by sulfadiazine,[1] nearly 70 medications have been reported to cause the syndrome. Since their introduction in the early 1950s, procainamide[2] and hydralazine[3] have been most closely linked to DIL, with clinical manifestations ranging from an asymptomatic increase in antinuclear antibody (ANA) titer[4,5] to multisystem organ involvement and death.[6] DIL generally occurs after months or years of drug therapy. It may manifest clinically as arthralgias, myalgias, fever, weight loss, pleural effusions, and, rarely, as pericarditis.[7] Laboratory evaluation usually reveals an elevated erythrocyte sedimentation rate (ESR), high ANA titers, and the presence of antihistone antibodies.[8]

The diagnosis of DIL is based on clinical suspicion, suggestive laboratory data, the temporal relationship between administration of a suspected agent and onset of symptoms, and the resolution of symptoms upon withdrawal of the agent.

β-Adrenergic receptor blocking agents in general are a rare cause of DIL, but reports to date have implicated such beta blockers as acebutolol,[9] atenolol,[10] labetolol,[11] metoprolol,[12] oxprenolol,[13] pindolol,[14] practolol,[15] propranolol,[16] and ophthalmic timolol.[17] Limited data are available, however, regarding the association of beta blockers with the pericardial manifestations of DIL.

We report the case of a patient with DIL related to the use of betaxolol hydrochloride; the patient's condition was complicated by pericarditis and a large pericardial effusion, and he was successfully treated with corticosteroid medications.

Report of a Case

An 82-year-old man was admitted to the Veterans Affairs Medical Center in Albuquerque with a 3-month history of weight loss, progressive dyspnea on exertion, pleuritic chest pain, and diffuse myalgias and arthralgias.

Chest x-ray showed a new right-sided pleural effusion and a lung ventilation-perfusion scan was read as "low probability" for pulmonary embolism. A test for ANA was positive, with a titer of greater than 1:640 and a homogeneous pattern. An ESR was elevated, at 61 mm/hour (normal range, 0–10 mm/hour). A transthoracic echocardiogram showed a normal ejection fraction and no evidence of pericardial effusion or thickening. Before admission, a further increase in right-sided pleural effusion was noted on chest x-ray. Thoracentesis of the effusion revealed a transudate. The anti–double stranded DNA antibody level was 9 IU/ml by enzyme-linked immunosorbent assay (normal level, <30 IU/ml).

The patient's medical history was significant only for hypertension. He did not smoke or drink alcohol and had not traveled recently. His family history was unremarkable. Since April 1991, he had been treated with 10 mg betaxolol hydrochloride daily. Other medications included amlodipine besylate (2.5 mg daily), oxybutynin chloride (5 mg daily), and salsalate (750 mg twice a day).

On admission, he was found to have a temperature of 103°F, blood pressure 117/75 mmHg, pulse 126, respiratory rate 20, and room air oxygen saturation 90%. Physical examination revealed an elderly man who was alert but in mild respiratory distress. There was no jugular venous distention, and peripheral pulses were normal. The patient was tachycardic with a normal S1 and S2; no murmur, pericardial friction rub, or gallop was noted. Pulmonary examination revealed decreased breath sounds in the right lower lung field. Bowel sounds were normoactive, and the abdomen was nontender. Extremities were without clubbing, cyanosis, or edema, and calves were symmetric and nontender. Except for chronic bony enlargement of the metacarpal-phalangeal joints, the remainder of the musculoskeletal examination was unremarkable.

An electrocardiogram obtained on admission showed sinus tachycardia with no ST or T wave changes. Chest x-ray revealed bilateral pleural effusions (larger on the right than on the left) and a normal cardiac silhouette. Initial laboratory evaluation showed white blood cell count, hematocrit, platelets, lactate dehydrogenase, and serum electrolytes within normal ranges; albumin was 3.1 g/dl (reference range, 3.8–5.0 g/dl); alkaline phosphatase was 120 U/l (reference range, 30–115 U/l); and urine analysis revealed 1+ protein.

The rheumatologic survey included the following: ANA titer >1:640; rheumatoid factor <20 IU/ml; antihistone antibody–positive; complement C3, 140 mg/dl (reference range, 85–200 mg/dl); complement C4, 41 mg/dl (reference range, 16–47 mg/dl). Anti–smooth muscle antibodies, anti-SSA, anti-SSB, anti-Jo-1, and anti-SCL-70 were all negative.

On day 5 after admission to the hospital, a pericardial friction rub was present across the precordium. Pulsus paradoxus was absent. A transthoracic echocardiogram revealed a large pericardial effusion with mild right atri-

(Hardee JT, Roldan CA, Du Clos TW. Betaxolol and drug-induced lupus complicated by pericarditis and large pericardial effusion. West J Med 1997 August; 167:106–109)

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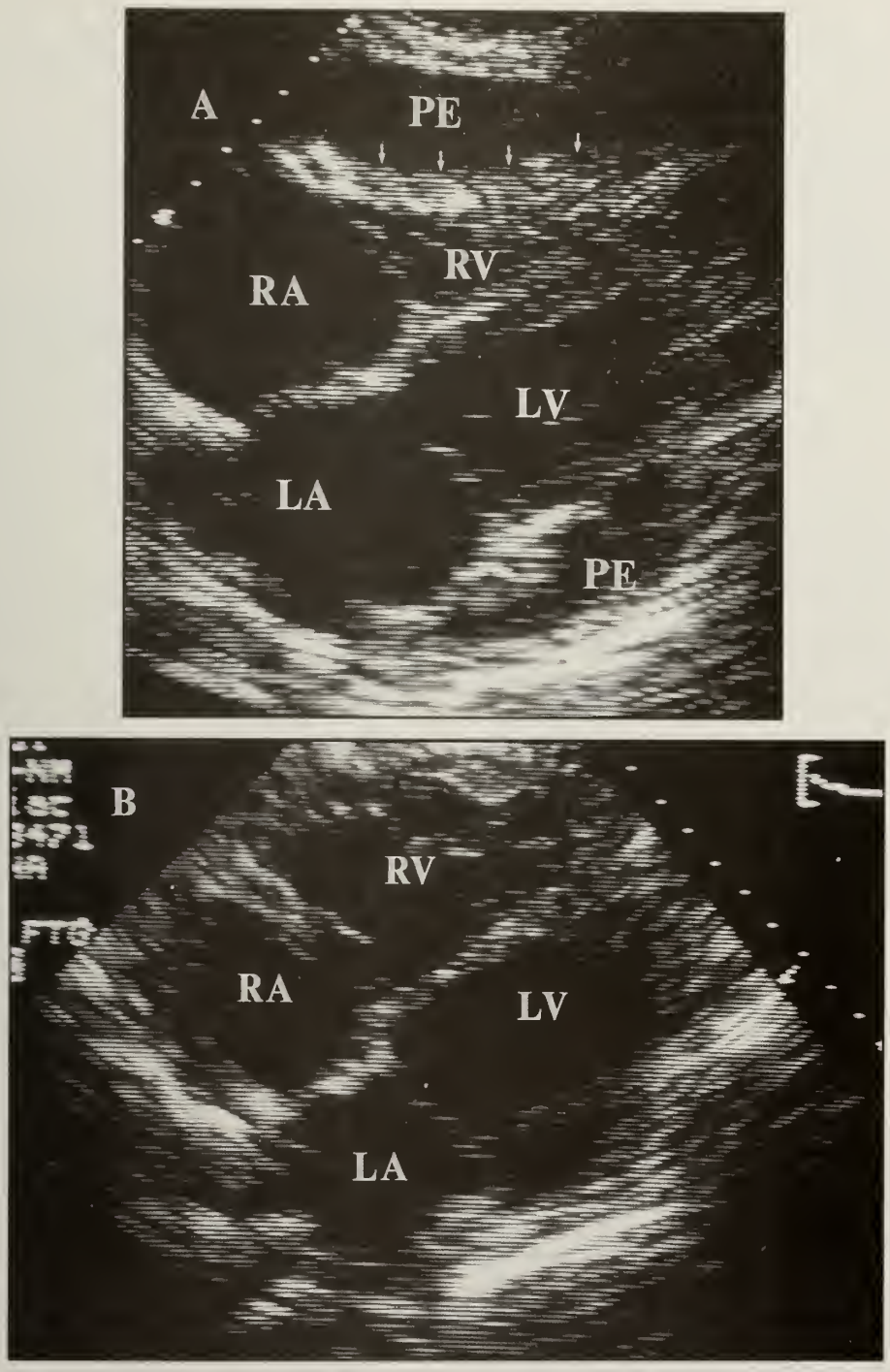

Figure 1.—This subcostal echocardiographic four-chamber view (A) shows a large anterior and posterior pericardial effusion (PE) with right ventricular (RV) diastolic collapse and evidence of visceral pericardial thickening (small arrows). RA = right atrium, LA = left atrium, LV = left ventricle. A repeated echocardiogram obtained after 4 days of steroid medication therapy (B) shows resolution of the pericardial effusion and the pericardial thickening.

al and right ventricular diastolic collapse, as well as an estimated right atrial pressure of 15 to 20 mmHg from the inferior vena caval dynamics (Figure 1A).

Betaxolol hydrochloride was discontinued, and 125 mg of methylprednisolone sodium succinate was administered intravenously to treat the suspected inflammatory pericardial effusion. Clinical improvement was seen within 24 hours as evidenced by resolution of the pericardial friction rub. A 3-day course of 125 mg intravenous methylprednisolone sodium succinate daily was

followed by a course of oral prednisone (20 mg daily). The amlodipine besylate dosage was increased to 5 mg daily for blood pressure control.

A repeated transthoracic echocardiogram obtained 4 days later showed resolution of the pericardial effusion with no evidence of right atrial or right ventricular diastolic collapse and normalization of right atrial pressures (Figure 1B). The patient was subsequently discharged, and a repeated transthoracic echocardiogram obtained 2 weeks later revealed continued resolution of the pericardial effusion. Prednisone therapy was discontinued, and the patient has since remained free of SLE-like symptoms.

Discussion

DIL is regarded as a rare variant of SLE, with a prevalence of 0.5 to 2.5 cases per 100,000 population.[18] Whereas the American College of Rheumatology has established specific clinical and laboratory criteria for the diagnosis of SLE,[19] the diagnosis of DIL is based on clinical suspicion, suggestive laboratory data, the temporal relationship between administration of a suspected agent and onset of symptoms, and the resolution of symptoms on withdrawal of the inciting agent. The peak incidence of SLE occurs between the ages of 15 and 40. Among patients with SLE, there is a female-to-male ratio of 9:1; in pediatric and elderly populations, the ratio approaches 2:1. DIL, on the other hand, occurs with similar frequency in male and female patients. Patients with DIL tend to be older than those with idiopathic SLE because the implicated medications are used more often in elderly patients.[17]

Clinical features of DIL include symmetrical, polyarticular arthralgias, which are generally nondeforming and not associated with significant joint effusion, in more than 80% of patients.[20] Diffuse myalgias affecting both distal and proximal muscles have been described in approximately 50% of cases.[21] Pulmonary involvement, manifesting as pleuritis, pleural effusion, or pulmonary infiltration, is seen in 15 to 50% of cases. Pericardial involvement is less common, being described in only 5 to 16% of cases.[18] Fever and weight loss have also been reported.[22,23] The classic malar rash, mucosal ulcers, and alopecia, which are common in SLE, are rare in DIL. Hepatomegaly, splenomegaly, renal involvement, and neuropsychiatric disorders are also unusual in DIL.[17]

Laboratory features seen with DIL include positive ANAs, which most frequently exhibit a homogeneous staining pattern and are seen in nearly 100% of cases. Antibodies to Sm antigen and double-stranded DNA, which are highly specific for SLE, are not present in DIL.[17] Although antihistone antibodies are characteristic of DIL and occur in 70 to 90% of cases, they may also be found in 50 to 80% of SLE cases.[24] Antihistone antibodies may be of the IgG or IgM type and can be targeted against individual histones, including H1, H2A, H2B, H3, and H4, or against histone complexes such as H2A-H2B and H3-H4.[25] The presence of immunoglobulin G antibodies to the H2A-H2B histone dimer is associated with symptomatic DIL.[26] In contrast to SLE, complement levels in DIL are generally normal. Erythrocyte sedimentation rates are elevated in approximately 90% of patients with DIL and usually return to baseline upon withdrawal of the offending agent and resolution of clinical symptoms.[22] Mild normochromic, normocytic anemia has been reported in rare cases, as have thrombocytopenia and leukopenia.[27]

A review of the literature, including a report of drugs recently associated with lupus syndromes,[28] failed to link betaxolol hydrochloride specifically to DIL. We attribute the above case to betaxolol hydrochloride because the symptoms we found to be associated with its use fit the clinical and laboratory as well as temporal diagnostic criteria for this disease. The patient's arthralgias, myalgias, pleural effusions, fever, weight loss, and pericarditis were consistent with the usual clinical findings in DIL. The elevated ESR and ANA titers as well as the presence of antihistone antibodies and the absence of anti–double stranded DNA antibodies helped us differentiate this diagnosis from that of idiopathic SLE. The time course from initiation of betaxolol hydrochloride treatment to onset of symptoms was also consistent with DIL in that most cases of this disease occur after months to years of therapy with the offending drug.

SLE sometimes presents with pericardial involvement,[29] and there are also a small number of case reports of DIL associated with pericarditis,[30] pericardial effusion,[31] and cardiac tamponade.[32–35] It is, however, extremely rare for DIL to present with pericarditis as the major initial symptom, and cardiac tamponade is also exceptional.[33] The pericardial effusions that occur with DIL range from small, hemodynamically insignificant fluid collections to large effusions causing tamponade. A case of cardiac tamponade associated with procainamide-induced DIL has been reported in which echocardiography showed a large effusion with phasic respiratory variation and a marked swinging of the heart within the pericardial sac.[36] Pericarditis in a case of procainamide-induced lupus revealed the presence of lupus erythematosus cells; a pericardial biopsy in that case demonstrated fibrinous pericarditis.[35]

As described in this case, rapid clinical improvement and resolution of pericardial effusion are usually observed in DIL after the offending drug is withdrawn and corticosteroid therapy is begun. Published reports have advocated administration of 40 to 60 mg of oral prednisone daily as the treatment of choice,[32,33] although no controlled trials have evaluated the use of corticosteroid medications in this particular clinical setting. The repeated echocardiogram obtained in our case after 4 days of intravenous steroid therapy (Figure 1B) showed striking improvement in the size of the patient's pericardial effusion as well as normalization of his hemodynamic parameters.

Physicians should be aware of DIL as a possible complication of β-adrenergic receptor blocker therapy. Clinical or laboratory evidence of DIL warrants further

diagnostic evaluation, including echocardiography and discontinuation of the offending agent, and may call for treatment with corticosteroid medications.

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Magnetic Resonance Imaging for the Diagnosis of Occult Pelvic Fractures: Two Case Reports

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THE USE OF MAGNETIC RESONANCE IMAGING (MRI) for detection of radiographically occult bone injuries is increasing. We present two cases of occult bone injuries to the pelvis that were detected by means of MRI after plain radiographs failed to reveal the injuries. In both cases, the patients had prolonged recovery periods that could not have been anticipated without the diagnosis of bone injury. The early diagnosis provided by MRI may lead to more accurate treatment decisions, fewer unnecessary tests and follow-up visits, and more-accurate prediction of the degree of physical disability and the length of time necessary for convalescence.

Physicians who work in emergency departments frequently evaluate patients who have pelvic pain after injury. With efforts to decrease emergency department use, primary care physicians may expect to see more patients with pelvic pain from minor injuries. The

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workup of patients with suspected pelvic fractures after blunt trauma is usually straightforward. Patients with pelvic pain or tenderness require pelvic radiographs to exclude the possibility of fractures. Patients with normal mental status and no pelvic pain have been shown to have an insignificant fracture rate and do not require routine films.[1] There is little or no literature regarding patients who have normal radiographs but persistent pain.

MRI has been shown to be extremely sensitive in detecting and characterizing occult injuries to bone.[2,3] These areas of presumed contusion and microfracture within the medullary portion of the bone are not visualized using plain radiographs and may also be missed by computed tomography if, as is often the case, the overlying cortical bone is intact. The usefulness of MRI in detecting these types of injuries has been well documented in sports medicine,[4,5] but its potential role in assessing pelvic trauma has not been emphasized. We present two emergency department patients in whom occult bone injuries to the pelvis were diagnosed by MRI after results of initial radiographs were negative.

Report of Two Cases

Case 1

A 43-year-old male athlete came to the emergency department after his bicycle slipped on ice at slow speed. As he fell, his buttocks slammed into the seat and he was unable to stand after the accident occurred. He complained of severe pelvic pain. Physical examination revealed bilateral buttock tenderness with normal strength and sensation in both legs, but the examination was incomplete because the patient's pain allowed only limited movement. While in the emergency department, the patient was given 60 mg of ketorolac via intramuscular injection, which provided some pain relief. An anteroposterior radiograph of the pelvis did not show any fracture. The patient was diagnosed with a strain or contusion and given nonsteroidal anti-inflammatory drugs (NSAIDs) for pain control.

After discharge from the hospital, the patient complained of severe persistent pain, and although he could move slowly with the use of crutches, he was still unable to stand without assistance. Three days later, a more careful examination suggested paralysis of muscles innervated by the right obturator nerve, but a second pelvic radiograph again showed no bone injury.

The patient was told to return to work by his employer. At the patient's insistence, however, an MRI of the pelvis was obtained, which revealed abnormal signal intensity in the pubic rami bilaterally as well as in the right sacral ala, findings compatible with bone contusions, occult fractures, or both (Figure 1A and B).

The patient required narcotic and NSAID pain medication for several weeks after the accident. His daily activities were limited, and he needed crutches to walk for 6 weeks after the injury. With full knowledge of the extent of his injuries, he canceled several risky athletic events in which he would otherwise have pushed himself to participate. He achieved full recovery by the end of 16 weeks.

Case 2

A 45-year-old woman was brought to the emergency department after being involved in a motor vehicle accident. Her car had been struck on the passenger side at a low to moderate speed, and her only complaint was right hip and pelvic pain. Physical examination revealed normal strength, sensation, and circulation in both legs with a stable, somewhat tender pelvis. An anteroposterior pelvic radiograph was normal. Because of her pelvic and hip pain, however, the patient was unable to stand. For this reason, further radiographs were obtained including right hip films, Judet views of the right hip, and lumbosacral spine views, none of which showed acute abnormality. The trauma surgery service insisted on discharging the patient from the emergency department, claiming that she was feigning her symptoms, but because of her persistent pain and inability to stand, an emergency department attending physician ordered a pelvic MRI. The MRI revealed abnormal signal intensity in the ischial rami bilaterally, the right pubic ramus, and right sacral ala, all of which was compatible with contusions or occult fractures in these regions (Figure 2A and B).

The patient suffered pain for a long time after her accident. She was unable to walk, stand, or use the bathroom without assistance for the first 2 weeks after injury. For 6 to 8 weeks, she required narcotic analgesics and NSAIDs along with crutches for ambulation. Because she was unable to perform her usual job, the patient was suspected of malingering by a company physician who had obtained her plain film reports. The disclosure of the MRI results to the physician led to a more realistic expectation of a prolonged recovery period. The patient believed that the objective evidence of the MRI kept her from losing her job.

Discussion

Plain radiographs are routinely ordered after trauma because they provide a rapid and cost-effective method for diagnosing most acute fractures. Unfortunately, a number of significant, symptomatic bone injuries, such as bone contusions, bruises, and microtrabecular fractures, are not detectable using plain films. Pelvic bone injuries are especially difficult to diagnose with plain radiographs because of the complex bone geometry and overlying bowel gas peculiar to this anatomical region. As illustrated by our two cases, an MRI in the acute setting can enable rapid diagnosis of these injuries because the associated edema or hemorrhage can be directly visualized within the medullary cavity. Also, unlike radionuclide scanning, the exquisite soft tissue contrast characteristic of the MRI technique allows accurate diagnosis of any concurrent soft tissue injuries.

Traditionally, MRI has not been used to detect acute bone fractures, primarily because of its relatively high cost and lack of availability. MRI is sensitive in detecting

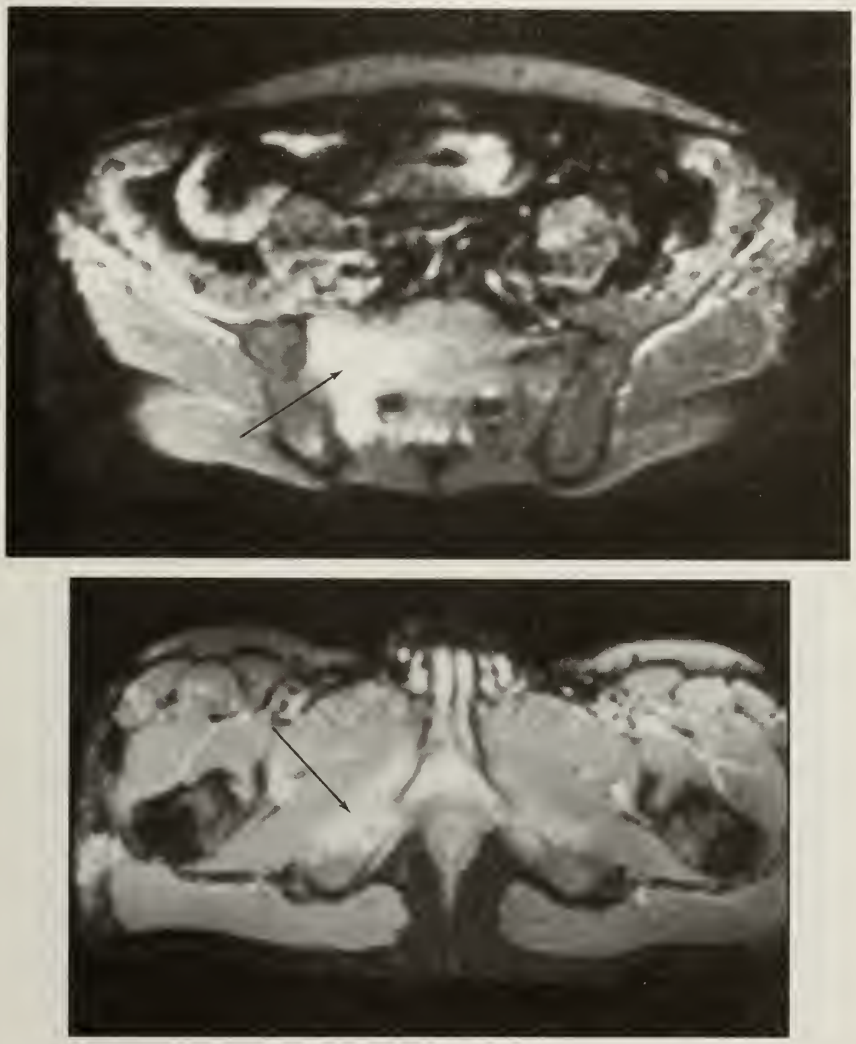

Figure 1.—Axial inversion recovery image (upper panel) demonstrating a large area of abnormally increased signal in the right sacral area compatible with a bone contusion/trabecular injury. Axial inversion recovery image at a more caudal level (lower panel) shows bilateral nondisplaced fractures of the inferior pubic rami with adjacent areas of high signal edema.

fracture-related edema and hemorrhage in the bone marrow and adjacent soft tissues, however, which makes it an excellent tool for detecting bone injuries that are often not apparent on initial radiographs. Several studies have demonstrated the ability of MRI to accurately diagnose stress fractures, which are traditionally difficult to identify, especially in their early stages.[6,7] Similarly, MRI shows promise in the acute detection of occult scaphoid fractures, which in the past has necessitated casting, repeated office visits, and radiographs.[8] MRI can also accurately diagnose occult hip fractures, allowing early surgical repair and reducing hospital stays and potential complications. By using a focused protocol, this imaging technique can be applied in a cost-effective manner.[9]

Radionuclide bone scanning also provides a proven, alternative method for investigating bony trauma. This modality, which demonstrates areas of bone turnover and repair, can be used to assess occult bone injuries. A scan takes 4 to 6 hours to complete, however, may be falsely negative in the first 48 to 72 hours after injury (especially in elderly patients), and does not provide direct visualization of soft tissue structures.

The cost differential between bone scanning and MRI is often used to justify the radionuclide examination. But in a small series of patients with hip fractures and indeterminate radiographs, limited use of MRI has been shown to be extremely accurate for diagnosis and cost-competitive with radionuclide scanning.[3]

Computed tomography (CT) scanning is another diagnostic alternative that may detect some occult fractures. If the overlying cortex is intact, however, or if the degree of trabecular disruption is not sufficient to be directly visualized, CT scanning fails to detect many injuries, such as contusions.[10]

Figure 2.—Axial T1 weighted image (upper panel) demonstrates a low signal intensity fracture line in the right sacral area not seen on plain films. Axial inversion recovery image at level of symphysis pubis (lower panel) shows high signal contusion in the left symphysis (arrow). Additional edema/hemorrhage is present in left adductor muscle, compatible with acute injury.

It could be argued that detecting these injuries is unnecessary, since doing so will not change many treatment plans that simply involve weight bearing as tolerated. This argument overlooks an important issue, namely, the patient's right to understand the full extent and consequences of his or her injury. The prolonged recovery periods required in both of our cases would not have been anticipated based on a diagnosis of simple soft tissue injury. This fact has a direct impact on worker's compensation issues such as the predicted length of convalescence required before returning to work. Furthermore, the additional costs associated with the multiple follow-up radiographs required for each patient in our two cases, and with the return visit to the emergency department in one of these cases, might have been avoided had the MRI been performed earlier.

A primary goal of efficient medical care is to obtain an accurate diagnosis on the initial visit whenever possible, thereby reducing the need for splinting, follow-up radiographs, and repeated office or emergency department visits. In this sense, although it seems somewhat paradoxical, a negative MRI obtained in a symptomatic patient at an early stage may actually improve the cost-effectiveness of the workup (and hence of the treatment as a whole) by eliminating the need for these follow-up measures.

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Poem

Physical

JOHN DONOGHUE, *Cleveland Heights, Ohio*

It's *nothing*, he says, a small asymmetry, we'll check it out
when you get back. The worst, is that it's cancer;
the best, is that it's just you.
Is he *crazy*? When I get *back*?—the million dollar rented beach house
turned to stomach acid?! *Do—it—now*! I shout,

shaking him, let's check it out *yesterday*!, this town bursting
with urologists just sitting on their hands—where they rest them
when they're idle. (Friends, have physicals in Fall,
with nothing planned.)

A small asymmetry. A bad sign for one who's been symmetric
all his life—write with the right, throw with the left,
when praised, quick to name a fault.
That's *balance*, he says, not symmetry, and on his pad
he draws a circle. Prostate—the size of a walnut,

pale, firm, partly muscle partly gland, a fist
at the base of the urethra, and *yours*, he says, is slightly
asymmetric—on his circle he draws a bulge
from 12 to 3. You're *fine*! It's *nothing*! *Relax*!

And what *would* I have him do? Cry out, *Oh, no*!
when he felt me? And he's right, it *is* balance we're after,
not symmetry, not that static, sentimental same-old same-old
across a boundary—one side unable to give
or teach anything to the other—our deep dislike of symmetry
the reason we marry opposites, not clones, the reason one foot

is always larger than the other, one heart, one lopsided stomach,
the reason first there's A, then B, the reason one-fourth of my walnut—
from 12 to 3—struck out on its own and bulged
into asymmetry. So . . . o.k. . . . I'll go. It *is* nothing.

I'll put on my Ray-Ban Cats, rub on my #20 Bain de Soleil.
I'll put on my aqua Speedo trunks and my black Rockport thongs.
I'll put on my Speigel rugby shirt, and my Yankees baseball hat.
I'll carry my red aluminum beach chair and reed mat
under my left arm, and my all-cotton towel and rainbow umbrella

under my right. I'll carry my cooler bag and my book bag
over opposite shoulders, and carefully, it being just myself,
I'll walk my newly strange asymmetric body—feeling now
like a threat—down to the sea.

Lessons From the Practice

Serendipity

JAMES C. NEELY, MD, *San Francisco, California*

It is defined as the gift of finding valuable or agreeable things not sought for. It is Einstein inventing relativity while watching moving trains, Darwin in the Galapagos conceiving evolution in the flights of finches, Fleming accidentally noting the effects of penicillin mold on a colony of bacteria in a petri dish. Those who labor in the vineyard of original research do so in the faint hope that they too will experience a moment of epiphany that leads to an original contribution to science and the betterment of humankind. I was fortunate enough to have this happen to me, and in a most remarkable—indeed, serendipitous—way.

Thirty years ago, while still a resident in surgery, I was offered a summer job at the HF Bar Dude Ranch near Buffalo, Wyoming, as ranch doctor. Cowboys and dudes were always getting thrown from their horses, being kicked, or landing fishhooks in their eyes or ears. They needed somebody to handle the trauma, in addition to the myriad hangovers and cases of cabin fever. All this I did somewhat condescendingly but with good humor and professional aplomb. In truth, I was bored by the medical inconsequentiality of it all and I became an incorrigible dreamer.

There are not many places in this world more beautiful than the eastern foothills of the Little Big Horn Mountains in June. At the HF Bar Ranch, there was a plethora of young children, boys and girls, whose youthful parents were more than happy to unload their offspring on the reliable young doctor while they went off on other pursuits. The foothills seemed an obvious candidate for educational expeditions, so each day my young charges and I set out on horseback to explore this enchanting area. One day, around high noon, the two children at the head of our column spotted a deer and chased it through a ravine to a trail that opened suddenly onto a deep pit wedged between four large rocks. There before us, piled high as the eye could see, were the broken and scattered skeletons of scores, perhaps hundreds, of deer. I had heard of elephants going secretively off to their hidden mass graves to die, but until now I had never suspected that deer did this as well. With the sun high overhead, we were able to see the eburnated bones with a peculiar shining clarity that the light would not have afforded a mere half hour earlier in the day. It was an amazing sight, as if the light had struck our own private Stonehenge, revealing an ancient secret.

The children were thrilled and anxious to gather up the bones and take them home, perfect souvenirs of their time out West. But we were not prepared to undertake this task on such short notice, and I was also worried about disease. I promised them that if they kept our little secret we would return the next day and begin collecting the bones. My idea was to try to assemble a deer skeleton and at the same time teach the children some anatomy. So every day for a month or so we returned to the mass grave at the same time of day, picked out the bones we needed to complete our project, and brought them back to be assembled in my cabin—until finally we had put together what to my untutored anthropological eye seemed a pretty damned fine deer skeleton.

I tell this tale of my long hot summer days as the "Catcher in the Rye" only to illustrate how serendipity was working its slow, subtle wiles on me in ways that would eventually lead to my one good research idea of a lifetime. As we traipsed back and forth on horseback with the bones hanging from our saddles and rattling in the wind like some ghoulish mobile, I found myself thinking about human calcium metabolism. In those days physicians were seeing a lot of stomach and duodenal ulcers in people whose parathyroid glands had become overgrown or involved with tumors, causing the parathyroid hormone to be secreted in overabundance. It was generally accepted at this time that the excess parathyroid hormone somehow acted directly on the stomach to cause an increase in gastric acid secretion, which in turn caused ulcers. As I mused over the deer bones, I recalled that the parathyroid gland also regulated calcium metabolism; since an overactive parathyroid also caused an elevation in the circulating blood calcium level, it occurred to me that it was perhaps the calcium, not the hormone, that affected the stomach in such a way as to cause gastric hypersecretion and hence ulcers. Such was my rare moment of epiphany as I watched the sun spread out its colors magnificently and sink slowly behind the Big Horns that day. This moment would eventually lead to my discovery of the now well-established fact that hypercalcemia does indeed directly cause gastric hypersecretion and predisposes people to stomach ulcers. But for now I only had the idea; it still had to be proven.

By extreme good fortune, I was soon given a research award fellowship at the University of California in San

(Neely JC. Serendipity. West J Med 1997 August; 167:115–116)

Francisco and the munificent sum of $10,000 to work with. I had two years in which to complete my study, barely enough time for the research involved in such a major undertaking. My idea was to establish a group of dogs that had pouches like those Pavlov had described, in which gastric secretion could be measured. After 8 months, I had established a colony of 25 healthy dogs, all with little pouches hanging out at their sides, which I dutifully emptied at regular intervals in order to measure the gastric contents. The animals received a constant, consistent diet, and their normal daily baseline acid secretion was established for 3 months. Then vitamin D, which is known to increase calcium levels in the blood by enhancing intestinal absorption of calcium from foods, was given by injection to each dog until the blood calcium rose above normal levels, at which point the vitamin D was discontinued and the blood calcium level allowed to coast back to normal over a month or two. All the while, daily gastric pouch secretions were measured for changes.

My colleagues and I were a year and a half into the experiment, which was going beautifully, when the worst thing imaginable happened. The dogs became stricken with distemper, which spread through the colony like a brushfire. One by one they keeled over and died. There was absolutely nothing I could do. I was heartbroken. The animals (and with them sixteen months' worth of painstaking work) were wiped out—all of them, that is, except one precious dog, a boxer we called Strong because of the special pungency of his urine. Both the world and I owe Strong a debt of gratitude for surviving, because although only this dog remained, he was enough to allow us to complete the experiment. We were able to show that as his calcium levels increased, so did his gastric acid secretion, and as these levels gradually decreased, so did his daily pouch secretion. And because this was an experiment that extended over many months, carefully documented by daily measurements, Strong served as his own control, exhibiting a *before*, a *during*, and an *after* phase of blood calcium alterations.

When I excitedly took this result to the chairman of the department, he promptly eliminated all coauthorship, excluding my colleagues as well as his own name from the title page of my paper. He told me that I could submit my work anywhere I pleased, but on my own recognizance, without his sponsorship or imprimatur. After all, it was only one lousy dog. Nevertheless, that paper was accepted almost immediately in one of the most prestigious surgical journals. It was at this point that the chairman, without apology, suddenly saw fit to restore his name to the title page. Thus he taught me some basic truths about basic research.

But the good dog Strong's effort was the breakthrough, and mine was the seminal pilot study that inspired other researchers to prove definitively that hypercalcemia does indeed cause gastric hypersecretion and peptic ulceration of the stomach. For my part I quietly returned to surgery and undid Strong's pouch, hooked him up properly, and kept him as a prize pet, allowing him to father many pups until his natural death many years later. Still, in the twilight of my own career, it's high time the world heard of Strong and me and the children and the sunlight hitting just right on the bones of the deer in their secret mass grave that one summer high noon in Wyoming when an idea was born.

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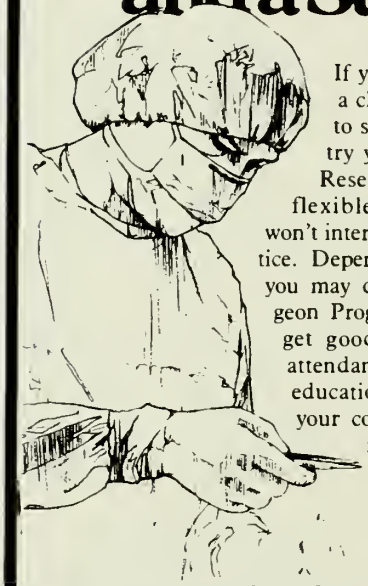

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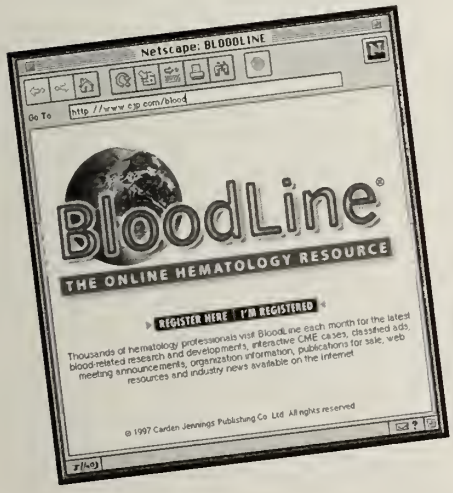

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OCTOBER 12 THROUGH OCTOBER 14, 1997

CALIFORNIA MEDICAL ASSOCIATION PROUDLY PRESENTS

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CREATING THE FUTURE OF HEALTH CARE

ACADEMY AGENDA

Sunday, October 12, 1997

1:00 pm REGISTRATION OPENS

3:00-3:40 pm ACADEMY WELCOME AND OPENING REMARKS

Welcome
H. Rex Greene, M.D., Leadership Academy Planning Committee Chair

Forecasting the 21st Century Physician: A Physician Leader's Predictions
Rolland C. Lowe, M.D., President, CMA
A Resident Leader's Predictions
Jay Udani, M.D., Chief Resident, Cedars Sinai Medical Center

A Student Leader's Predictions
Pamela Petersen-Crair, AMA Board, Student Trustee

3:40-4:20 pm **GENERAL SESSION 1:** Emerging Ethical Dilemmas for Physicians Payers and Purchasers
Emily Friedman, Writer, Lecturer, Health Policy Analyst and Ethicist

4:20-5:45 pm **PANEL DISCUSSION:** Physician-Assisted Suicide, End of Life and Managed Care: Ethical Challenges of the 90s
H. Rex Greene, M.D.

Alexander M. Capron, Topping Professor of Law, Medicine and Public Policy, School of Law, USC

Ernle W. D. Young, Ph.D., Co-Director, Center for Biomedical Ethics, Stanford University (Invited)

6:00 pm Cocktail Reception

Monday, October 13, 1997

8:00-8:45 **GENERAL SESSION 2:** Beyond Darwin: Introduction to the Evolving Competitive Health Care Marketplace
Steven Schroeder, M.D., President, Robert Wood Johnson Foundation

8:45-9:45 **PANEL DISCUSSION:** Megatrends and The Future of Managed Care
Patricia Powers, Executive Director, Pacific Business Group on Health

Arthur Southam, M.D., President & CEO, HealthNet

Robert Leibenluft, Assistant Director for Health Care, Federal Trade Commission

9:45-10:15 Coffee Break

10:15-11:15 **GENERAL SESSION 3:** What Will the Future Delivery System Look Like?
Peter Boland, Ph.D., President, Boland Health Care

James C. Robinson, Ph.D., Professor of Health Economics, University of California, Berkeley

11:15 - Noon **PANEL DISCUSSION:** The California Marketplace: Innovations, Opportunities and Threats
Nancy Oswald, Ph.D., Executive Director, National IPA Coalition

William Andereck, M.D., Chair, Solo & Small Group Practice Forum, CMA

Cal James, Principal, APM, Inc.

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The California Medical Association is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. The California Medical Association designated this continuing medical education activity for 15 credit hours, which may be applied toward the CMA Certification in Continuing Medical Education and the AMA Physician's Recognition Award.

We gratefully acknowledge the initial grant support of the following corporations for the development of CMA's Leadership Academy.
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Noon-1:30 Special Luncheon Presentation ***The Honorable Diane Feinstein*** (Invited)

1:30-3:15 pm **CONCURRENT BREAKOUT SESSIONS:**

SESSION A: Choices and Realities in Physician Practices–IPAs and Networks, Medical Groups, and Academic Centers
Francis J. Crosson, M.D., Executive Director, Permanente Federation

Mark Wagar, President, MedPartners, Inc.–Western Operations

Gerald S. Levy, M.D., Dean, UCLA School of Medicine

SESSION B: Essential Physician Leadership Skills

Who's Moving Up and Why
Susan Foster Reynolds, M.D., Ph.D., Managing Director, Physician Leader Practice, Russell Reynolds Associates, Inc.

The Well-Functioning Board
John Whitelaw, M.D., President, Sutter Medical Group

How to Build an Effective Physician Team
Richard T. Hoerl, Ph.D., M.P.A., Management Consultant, Hoerl & Associates

3:15-3:45 pm Afternoon Break

3:45-4:45 pm **GENERAL SESSION 4:** Universal Coverage: Ushering in an Era of Access
Jack Lewin, M.D., Executive Vice President & CEO, CMA

Sandra Hernandez, M.D., CEO, San Francisco Foundation; Former Director, San Francisco Department of Public Health

Christopher Jennings, Deputy Secretary to the President for Health Policy

4:45-5:45 **CONCURRENT BREAKOUT SESSIONS:**
SESSION C: Leading Edges of the California Access Agenda
Lois Salisbury, President, Children NOW

Steve Thompson, Vice President, Government Relations, CMA

Bruce Lee Livingston, Executive Director, Health Access

SESSION D: Physician Leadership Skills: Practice Management Issues
Richard T. Hoerl, Ph.D., M.P.A.

Catherine Hanson, J.D., Vice President & General Counsel, CMA

7:00-10:00 pm Western Steak Fry

Tuesday, October 14, 1997

8:00-9:00 **GENERAL SESSION 5:** Frontiers of Quality and Electronic Data Systems: Differentiating Fantasy from the Future
Robert Heller, Ph.D., Executive Vice President, Fair Isaac Company

Gordon Mosser, M.D., Institute for Clinical Systems Integration

9:00-10:15 **CONCURRENT BREAKOUT SESSIONS:**

SESSION E: Physician Responsibilities in the Quality Information Transformation
Gary Krieger, M.D., Vice Chair, American Medical Accreditation Program

Jill Silverman, President & CEO, Institute for Medical Quality

Robert Mittman, Director, Health Care Program, Institute for the Future

SESSION F: Physician Leadership Skills (Continued)

From Practicing Physician to Health Care Leader
Edward O'Neil, Ph.D., Co-Director, UCSF Center for Health Professions

Physicians as Elected Officials: Opportunities and Responsibilities
Diana D. Parnell, M.D., Chair, Marin County Healthcare District Board

10:15-10:45 Break

10:45-Noon **GENERAL SESSION 6:**
Robert Reid, MD, President-Elect, CMA

Creating The Future of Health Care: Two Perspectives
Mark Smith, M.D., M.B.A., President & CEO, California HealthCare Foundation

Reed Tuckson, M.D., President, Charles R. Drew University of Medicine & Science, Incoming Group Vice President, Professional Standards, AMA

Noon-12:10 pm **THE CHALLENGE AHEAD**
H. Rex Greene, MD

Jack Lewin, MD, EVP and CEO, CMA

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Western Journal of Medicine

INSTRUCTIONS FOR AUTHORS

In accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (URM), 1997

Our readers represent all branches of medicine. We wish to receive and publish manuscripts that are reliable and lively and that will improve the care of patients, the health of the public, or policies affecting either. Manuscripts should be of interest to a broad range of scholars, busy practitioners, students, and physicians in training who have a clinical orientation. The purpose of a paper or letter may be to report, inform, alert, review, and discuss, but, above all, to teach. Titles should be short and intriguing. Avoid the overuse of jargon, adverbs, and expendable words and phrases; use only standard abbreviations and acronyms; and use inclusive language (see AMA Manual of Style, 8th Edition). We appreciate your interest in The Western Journal of Medicine and our profession.

Manuscript Information

Manuscripts should be sent to the Editor, Linda Hawes Clever, MD, c/o Publisher, The Western Journal of Medicine, 1224 West Main Street, Suite 200, Charlottesville, VA 22903-2858. Manuscripts must be original, not previously published, and not under consideration by another publisher. If preliminary data were included in another presentation or publication, this should be noted in the cover letter, and a copy of that publication should be included. Any conflict of interest, actual or potential, should be revealed to the Editors (see Letter of Transmittal). Obtaining informed consent to protect patients' rights to privacy should be documented according to URM 1997.

All manuscripts should be double-spaced and, including references and abstract but not tables, should not exceed:

- Articles: 3,000 words (15 double-spaced pages)
- Conferences and Reviews: 3,000 words
- Topics in Primary Care Medicine: 3,000 words
- Case Reports, Alerts, and Notices: 1,500 words
- Commentaries: 2,000 words
- Lessons From the Practice: 1,000 words
- Letters to the Editor: 500 words

Manuscripts, except for Case Reports, Epitomes, and Lessons From the Practice, should include a nonstructured abstract of no more than 200 words summarizing the article. Abstracts should include a description of the purpose, design, patients, results, and conclusions.

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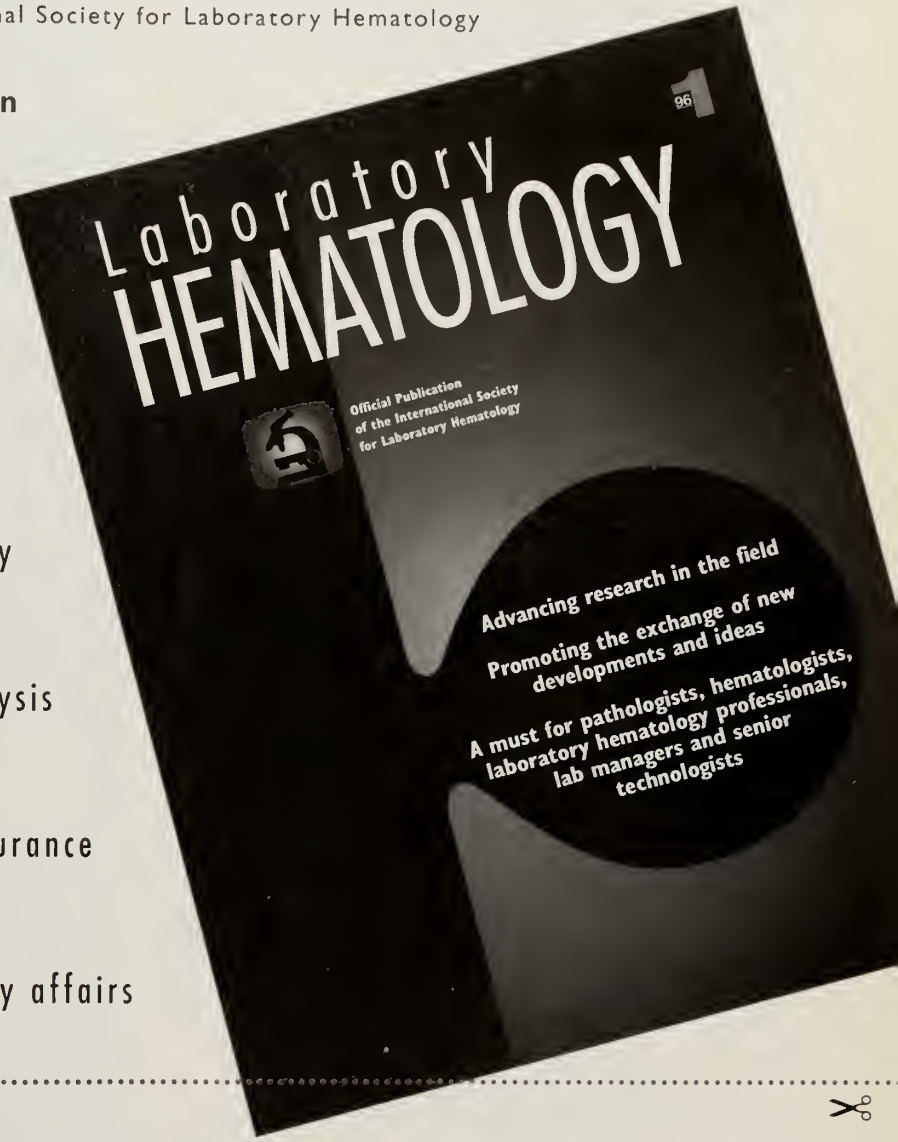

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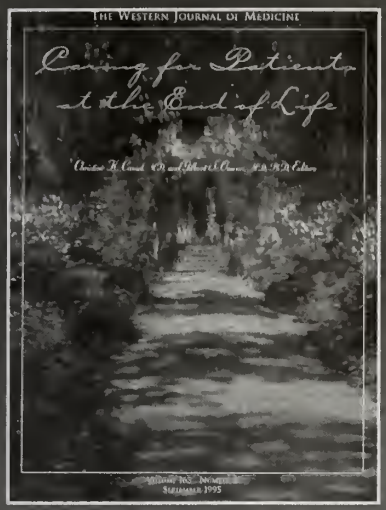

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VOLUME 167 • NUMBER 3 SEPTEMBER 1997

ARTICLES

138 Overcoming Social and Cultural Barriers to Care for Patients With Diabetes
J HUMPHRY, L JAMESON, and S BECKHAM

145 Rapid Hospital Discharge Following Laparoscopy for Ectopic Pregnancy—A Promise Unfulfilled?
L LEARMAN and D GRIMES

CONFERENCES AND REVIEWS

149 Fever, Rash, and Arthritis in a Woman With Silicone Gel Breast Implants
M GENOVESE

159 Scleroderma and Silicone Breast Implants
D WHORTON and O WONG

166 Insulin Signaling
M GOALSTONE and B DRAZNIN

EPITOMES

174 Important Advances in Family and General Practice

ALERTS, NOTICES, AND CASE REPORTS

180 Subarachnoid Hemorrhage at High Altitude
J LITCH, B BASNYAT, and M ZIMMERMAN

EDITORIAL

182 Plaintiffs, Defendants, Lawyers, and Lawyers: Facts and Rumors About Silicone
J SERGENT

CORRESPONDENCE

184 Pulmonary Edema Following a Licorice Binge
J CHAMBERLAIN and I ABOLNIK

185 Food Poisoning in Flight
A GODIL and F GODIL

OTHER FEATURES

130 Subscription Information

133 Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming

186 Classified Advertising

189 Instructions for Authors

Detailed Table of Contents: 131, 132

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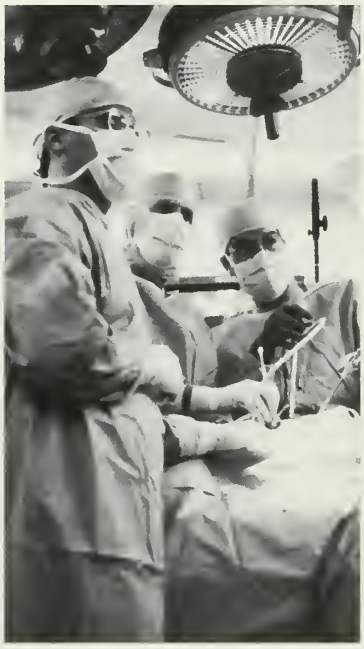

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WJM10

The Western Journal of Medicine

VOLUME 167 • NUMBER 3 • SEPTEMBER 1997

CONTENTS

ARTICLES

138 **Overcoming Social and Cultural Barriers to Care for Patients With Diabetes**

JOSEPH HUMPHRY, MD, FACP; LOLANI M. JAMESON, MPH; and SHEILA BECKHAM, RD, MPH, CDE

From the Waianae Coast Comprehensive Health Center, Waianae, Hawaii.

145 **Rapid Hospital Discharge Following Laparoscopy for Ectopic Pregnancy—A Promise Unfulfilled?**

LEE A. LEARMAN, MD, PhD, and DAVID A. GRIMES, MD

From the Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, School of Medicine.

CONFERENCES AND REVIEWS

149 **Fever, Rash, and Arthritis in a Woman With Silicone Gel Breast Implants**

MARK C. GENOVESE, MD

From the Division of Immunology and Rheumatology, Stanford University Medical Center, Stanford, California.

159 **Scleroderma and Silicone Breast Implants**

DONALD WHORTON, MD, MPH, and OTTO WONG, ScD

From Applied Health Sciences, San Mateo, California.

166 **Insulin Signaling**

MARC L. GOALSTONE, MD, and BORIS DRAZNIN, MD, PHD

From the Research Service and the Department of Medicine, Denver Veterans Administration Medical Center, and the University of Colorado Health Sciences Center.

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EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Family and General Practice

Items of progress in family and general practice. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance.

174 **Advances in Dementia Management**

JOHN F. RANDOLPH, MD

175 **Treatment for Human Immunodeficiency Virus (HIV) Infection**

SCOTT EBERLE, MD

176 **Advances in Diabetes Management**
THEODORE G. GANIATS, MD

177 **Bisphosphonates in the Treatment of Osteoporosis**
BRUCE J. DREYFUSS, MD, AND DALJEET S. RAI, MD

178 **Obesity as a Chronic Disease**
JOSEPH E. SCHERGER, MD, MPH

ALERTS, NOTICES, AND CASE REPORTS

180 **Subarachnoid Hemorrhage at High Altitude**
JAMES A. LITCH, MD, DTM&H; BUDDHA BASNYAT, MD; AND MARK ZIMMERMAN, MD
From the Himalayan Rescue Association, Nepal International Clinic, and Patan Hospital, Kathmandu, Nepal.

EDITORIAL

182 **Plaintiffs, Defendants, Lawyers, and Lawyers: Facts and Rumors About Silicone**
JOHN S. SERGENT, MD
From the Vanderbilt Medical Group, Vanderbilt University Medical Center, Nashville, Tennessee.

CORRESPONDENCE

184 **Pulmonary Edema Following a Licorice Binge**
JAMES J. CHAMBERLAIN, MD, and IGOR Z. ABOLNIK, MD

185 **Food Poisoning in Flight**
ASLAM GODIL, MD and FOUZIA GODIL, MD

OTHER FEATURES

130 WJM Subscription Information

133 Continuing Medical Education Activities

186 Classified Advertising

189 Instructions for Authors

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Medical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

Continuing Medical Education

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale. (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (520) 626-7832; (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Paulette Richardson, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-3387. For more information on accreditation or certification, please write to the above address.

ALLERGY

January 18–23, 1998—**36th Annual Scientific Session of The Western Society of Allergy and Immunology.** Four Seasons Resort, Wailea in Maui, Hawaii. For more information contact Rebecca Gough, Exec. Administrator, PO Box 1122, Roanoke, Texas, 76262; (817) 491-2616, Fax (817) 491-2241.

ANESTHESIOLOGY

November 14–16—**9th Annual Anesthesiology Update, 1997.** UC Davis at Monterey Plaza Hotel. Fri.–Sun. Contact: (916) 734-5390.

January 7–10, 1998—**UCSD Anesthesiology Update 1998.** UCSD at Hotel del Coronado, San Diego. Wed.–Sat. 18 hrs. Contact: Carol Heil (619) 543-2188.

CARDIOLOGY

October 16–18—**21st Annual Cardiology Update 1997.** American College of Cardiology at Carmel Valley Ranch Resort. Thurs.–Sat. 12 hrs. Contact: ACC Registration Secretary, Extramural Programs Dept. ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814-1699. (800) 253-4636, ext. 695.

December 12–14—**15th Annual Advances in Heart Disease.** American College of Cardiology at Grand Hyatt on Union Square San Francisco. Fri.–Sun. 16 hrs. Contact: ACC Registration Secretary, Extramural Programs Dept., (800) 253-4636, ext. 695.

January 16–17, 1998—**Radiotherapy to Reduce Restenosis.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri.–Sat. 16.5 hrs. Contact: Laurel Steigerwald, Scripps Clinic Dept. Academic Affairs 403c, 10666 N. Torrey Pines Road, La Jolla, 92037 (619) 554-8556.

January 30–February 1, 1998—**Clinical Nuclear Cardiology: Case Review With the Experts.** American College of Cardiology at Cedars-Sinai Medical Center, Los Angeles. Fri.–Sun. 19 hrs. Contact: ACC Registration Secretary, Extramural Programs Dept., (800) 253-4636, ext. 695.

February 19–21, 1998—**Cardiovascular Health: Coming Together for the 21st Century.** UCSF at Hyatt Regency Embarcadero San Francisco. Thurs.–Sat. Contact: UCSF.

COMPUTER TECHNOLOGY

September 25–27—**Computer Training for Physicians.** UCSD at National University San Diego. Thurs.–Sat. 18 hrs. $575. Contact: OCME (619) 534-3940.

October 17–19—**Computer Training for Physicians.** UCSD at National University San Diego. Thurs.–Sat. 18 hrs. $575. Contact: OCME (619) 534-3940.

November 20–22—**Computer Training for Physicians.** UCSD at National University San Diego. Thurs.–Sat. 18 hrs. $575. Contact: OCME (619) 534-3940.

December 11–13—**Computer Training for Physicians.** UCSD at National University San Diego. Thurs.–Sat. 18 hrs. $575. Contact: OCME (619) 534-3940.

January 28–31, 1998—**Medicine Meets Virtual Reality: Art, Science, Healthcare Evolution.** UCSD at San Diego Hyatt Regency. Wed.–Sat. Contact: Karen Morgan (760) 751-8841.

DERMATOLOGY

September 27–28—**The Skin From A to Z.** UCSF at Laurel Heights Campus, UCSF. Sat.–Sun. 10 hrs. $275. Contact: UCSF.

January 15–18, 1998—**Practical Dermatology for the Primary Care Physician.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency La Jolla, San Diego. Method, AV, L, SB, W. $575. Thurs.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

January 31–February 1—**Melanoma 1998: 8th Annual Cutaneous Malignancy Update.** Scripps Clinic at Scripps Memorial Hospital, La Jolla. Sat.–Sun. 11.5 hrs. Contact: Jill Hofmans, Scripps Clinic, (619) 554-8556.

May 3–6, 1998—**Practical Dermatology for the Primary Care Physician.** Las Vegas. Sponsored by Continuing Medical Education Associates. Caesar's Palace Las Vegas. Method, AV, L, SB, W. $575. Sun.–Wed. 20 hrs. credit: AMA, AOA, AAP, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

EMERGENCY MEDICINE

October 16–18—**16th Annual Recent Advances in Pulmonary & Critical Care.** UCSF at Palace Hotel San Francisco. $495. Thurs.–Sat. 17 hrs. Contact: UCSF.

October 17–19—**Essentials in Emergency Medicine and Urgent Care.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency La Jolla, San Diego. Method, AV, L, SB, W. $495. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

October 20–24—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon.–Fri. 32 hrs. $495. Contact: OCME (619) 534-3940.

October 27–31—**26th Annual Topics in Emergency Medicine.** UCSF at Radisson Miyako Hotel San Francisco. $725. Mon.–Fri. 32 hrs. Contact: UCSF.

November 10–14—**Emergency Medicine Symposium II.** UCSD at La Jolla Marriott. Mon.–Fri. 32 hrs. $495. Contact: OCME (619) 534-3940.

December 15–19—**Emergency Medicine Symposium II.** UCSD at UCSD San Diego. Mon.–Fri. 32 hrs. $495. Contact: OCME (619) 534-3940.

February 16–20, 1998—**Emergency Medicine Symposium I.** UCSD at La Jolla Marriott San Diego. $495. Mon.–Fri. 32 hrs. Contact: OCME (619) 534-3940.

FAMILY PRACTICE/PRIMARY CARE

September 20—**Health for the 21st Century (Women's Health in 1997).** UCSD at Town and Country, San Diego. Sat. 5 hrs. Contact: Kurt Benirschke (619) 534-2618.

September 25–27—**HIV, AIDS & Women.** OCME at La Jolla Marriott, San Diego. Thurs.–Sat. 14 hrs. $175. Contact: OCME (619) 534-3940.

September 27–30—**OB/GYN Review.** USC at Red Lion Hotel, Glendale. Sun.–Tues. 38 hrs. Contact: USC.

September 27—**2nd Annual Women's Health Symposium.** UCD at Davis Medical Center, Sacramento. Sat. Contact: UCD.

October 2–4—**Primary Care Orthopaedics.** UCSD at Hyatt Regency, La Jolla. Thurs.–Sat. 15 hrs. $575. Contact: OCME (619) 534-3940.

October 4—**Stroke Update: Critical Issues for the Primary Care Physician.** Alta Bates Medical Center at Haas School of Business, UC Berkeley. $135. Sat. 6.15 hrs. Contact: Caroline Carey (510) 204-3884.

October 15–17—**12th Annual Primary Care Medicine: Principles and Practice.** UCSF at Cathedral Hill Hotel San Francisco. $525. Wed.–Fri. 20 hrs. Contact: UCSF (415) 476-5208.

November 20–22—**Women's Health Issues in Primary Care.** UCSD at Hyatt Regency, La Jolla. Thurs.–Sat. 18 hrs. $300. Contact: OCME (619) 534-3940.

May 15–19, 1998—**Primary Care Essentials.** San Francisco. Sponsored by Continuing Medical Education Associates. Grand Hyatt on Union Square San Francisco. Method, AV, L, SB, W. $750. Fri.–Tues. 32 hrs. credit: AMA, AOA, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

GERIATRICS

November 10–12—**Geriatrics Update, 1997.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $475. Mon.–Wed. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

INFECTIOUS DISEASE

September 25–27—**HIV, AID & Women.** OCME at La Jolla Marriott, San Diego. Thurs.–Sat. 14 hrs. $175. Contact: OCME (619) 534-3940.

November 7–9—**Advances in Infectious Disease.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $475. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

February 6–7, 1998—**16th Annual Infectious Disease Conference.** UC Davis Medical Center at Sacramento Hilton Inn. Fri.–Sat. Contact: (917) 734-5390.

INTERNAL MEDICINE

September 26–30—**Internal Medicine 1997—Fall Program.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $675. Fri.–Tues. 30 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

November 22—**Management of Dyspepsia, Peptic Ulcer Disease and Gastric Cancer.** Sat. 4 hrs. $20. Contact: OCME (619) 534-3940.

March 20–26, 1998—**Internal Medicine 1998.** San Diego. Sponsored by Continuing Medical Education Associates. Hotel del Coronado San Diego. Method, AV, L, SB, W. $795. Fri.–Thurs. 45 hrs. credit: AMA, AOA, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

NEPHROLOGY

January 29–31, 1998—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at La Jolla Marriott. Thurs.–Sat. 17 hrs. $425.

NEUROLOGY

October 16–17—**Neuroradiology Update.** Thu.–Fri. Hotel Del Coronado, Coronado, California. $300. Sponsored by UC San Diego. Information: Ryals & Associates, Inc., PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773; Fax: (770) 552-9859; http://www.ryalsmeet.com.

October 20–22—**Neurology and Outpatient Psychiatry in Primary Care.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency La Jolla, San Diego. Method: AV, L, SB, W. $495. Mon.–Wed. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

October 25—**"Brain Attack!" '97.** UCLA Stroke Center at Beverly Hilton, Beverly Hills. Sat. 6.5 hrs. Contact: Office of CME (310) 794-2620.

February 11–13, 1998—**Recent Advances in Neurology.** UCSF at Fairmont Hotel San Francisco. Wed.–Fri. 15 hrs. Contact: UCSF (415) 476-4251.

NEUROSURGERY

October 11–15—**1996-1997 Temporal Bone Surgical Dissection Courses.** The House Ear Institute at Los Angeles. Sat.-Wed. 48 hrs. $1,300. Contact: House Ear Institute, 2100 W. Third St., Los Angeles 90057. (213) 483-4431, ext. 7079.

November 1–5—**1996-1997 Temporal Bone Surgical Dissection Courses.** The House Ear Institute at Los Angeles. Sat.-Wed. 48 hrs. $1,300. Contact: House Ear Institute, 2100 W. Third St., Los Angeles 90057. (213) 483-4431, ext. 7079.

OB/GYN

February 12–15, 1998—**Office Gynecology and Women's Health for the Primary Care Physician.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Islandia San Diego. Method, AV, L, SB, W. $575. Thurs.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 28–March 3, 1998—**15th Annual OB/GYN Update: 1998.** UC Davis Medical Center at South Lake Tahoe. Sat.–Tues. Contact: (917) 734-5390.

OCCUPATIONAL & ENVIRONMENTAL

October 20–24—**Occupational & Environmental Medicine IV.** UCSF at Radisson Miyako Hotel San Francisco. $725. Mon.–Fri. 40 hrs. Contact: UCSF (415) 476-5208.

ONCOLOGY

October 25—**Interventional Approach to Cancer Care.** St. Mary Medical Center at Holiday Inn Victorville. Sat. 8 hrs. $90. Contact: Yvonne Newton, CTR, St. Mary Regional Medical Center, 18300 Highway 18, Apple Valley, 92307 (760) 242-2311, ext. 6111.

December 7—**103rh Semi-Annual Seminar: Cutaneous Neoplasms.** California Tumor Tissue Registry at Sheraton Palace Hotel San Francisco. $265. Sun. 8 hrs. Contact: Loma Linda University (909) 824-4788.

January 16–17, 1998—**Radiotherapy to Reduce Restenosis.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri.–Sat. 16.5 hrs. Contact: Laurel Steigerwald, Scripps Clinic Dept. Academic Affairs 403c, 10666 N. Torrey Pines Road, La Jolla, 92037 (619) 554-8556.

February 16–19, 1998—**Clinical Hematology & Oncology.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel La Jolla. Fri.–Mon. 24 hrs. Contact: Laurie A. Regis, Scripps Clinic (619) 554-8556.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Education Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education, (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

ORTHOPEDICS

April 23–26, 1998—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency San Francisco. Method, AV, L, SB, W. $575. Thurs.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

May 3–6, 1998—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Las Vegas. Sponsored by Continuing Medical Education Associates. Caesar's Palace Las Vegas. Method, AV, L, SB, W. $575. Sun.–Wed. 20 hrs. credit: AMA, AOA, AAP, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

OTOLARYNGOLOGY

October 11–15—**1996–1997 Temporal Bone Surgical Dissection Course.** House Ear Institute at Los Angeles. Sat.–Wed. 48 hrs. $1,300. Contact: House Ear Institute (213) 483-4431.

November 1–5—**1996-1997 Temporal Bone Surgical Dissection Course.** House Ear Institute at Los Angeles. Sat.–Wed. 48 hrs. $1300. Contact: House Ear Institute, 2100 W. Third St., Los Angeles, CA 90057. (213) 483-4431, ext. 7079.

PEDIATRICS

September 18–21—**Practical Pediatrics.** American Academy of Pediatrics at Fairmont Hotel, San Francisco. Thurs.–Sun. 19 hrs. $495. Contact: AAP P.O. Box 77-2862, Chicago, IL 60678-2862 (800) 433-9016 ext. 6796 or 7657.

September 25–27—**The Fetus & Newborn: State-of-the-Art Care.** Contemporary Forums at Hotel del Coronado, San Diego. Thurs.–Sat. 16 hrs. $415. Contact: Contemporary Forums, 11900 Silvergate Drive, Dept. 348, Dublin, CA, 94568. (510) 828-7100, ext. 0.

October 25–28—**Pediatric Facial Plastic Surgery.** UCD at Monterey Plaza Hotel. Sat.–Tues. Contact: UCD.

December 6–7—**Stabilization and Management of Critically Ill Child.** UCSF at Embarcadero Hyatt Regency Hotel San Francisco. Sat.–Sun. Contact: UCSF (415) 475-4251.

January 24, 1998—**Update in Behavioral/Developmental Pediatrics.** UCSF at campus of UCSF. Sat. Contact: UCSF.

February 6–11, 1998—**PREP the Course.** AAP at Fairmont Hotel San Francisco. Fri.–Wed. 44 hrs. Contact: AAP (800) 433-9016, ext. 6796 or 7657.

February 15–18, 1998—**Pediatrics Update 1998.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Islandia San Diego. Method, AV, L, SB, W. $575. Sun.–Wed. 20 hrs. credit: AMA, AOA, AAP, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 16–19, 1998—**Clinical Hematology and Oncology: 1998.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel La Jolla. Fri.–Mon. 24 hrs. Contact: Laurie A. Regis, Scripps Clinic (619) 554-8556.

PSYCHIATRY

November 14–16—**43rd Annual Group Therapy Symposium.** UCSF at Mark Hopkins Hotel, San Francisco. Fri.–Sun. 20 hrs. $340. Contact: UCSF.

PSYCHOLOGY

October 18—**An Update on New Treatment Advances for Schizophrenia.** UC Davis Medical Center at UC Davis Cancer Center Auditorium, Sacramento. $55. Sat. 4 hrs. Contact: UC Davis Medical Center (916) 734-5390.

RADIOLOGY

September 20–21—**Ultrasound Update: 1997.** UCD at DoubleTree Hotel, Sacramento. Sat.–Sun. Contact: UCD.

October 14–18 & 21–25—**Nuclear Medicine Mini-Fellowship.** UCSD at UCSD Medical Center. Tues.–Sat. 44 hrs. $3,000. Contact: David Yeung (619) 534-6682.

October 16–17—**Neuroradiology Update.** Thu.–Fri. Hotel Del Coronado, Coronado, California. $300. Sponsored by UC San Diego. Information: Ryals & Associates, Inc., PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773, Fax: (770) 552-9859, http://www.ryalsmeet.com.

October 17–19—**17th Annual Comprehensive Review of Vascular & Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Fri.–Sun. 14.5 hrs. $325. Contact: Ryals & Assoc. (770) 641-9773.

October 20–24—**Multispecialty Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon.–Fri. Contact: Ryals & Assoc. (770) 641-9773.

October 20–24—**22nd Annual San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon.–Fri. Contact: Ryals & Assoc. (770) 641-9773.

October 22–26—**Musculoskeletal MR.** Wed.–Sun. The Westin Resort Hotel, Hilton Head, SC. $550. Sponsored by UC San Diego. Information: Ryals & Associates, Inc., PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773; Fax: (770) 552-9859; http://www.ryalsmeet.com.

January 16–17, 1998—**Radiotherapy to Reduce Restenosis.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri.–Sat. 16.5 hrs. Contact: Laurel Steigerwald, Scripps Clinic Dept. Academic Affairs 403c, 10666 N. Torrey Pines Road, La Jolla, 92037 (619) 554-8556.

SURGERY

September 19–20—**3rd Annual Surgical Review: Update in Minimally Invasive Surgery, Trauma and Ultrasound.** UCD at David Grant Medical Center, Fairfield. Fri.–Sat. Contact: UCD.

October 4–5—**New Directions in Lasers & Cosmetic Surgical Procedures: A Hands-On Course.** UCD at UC Davis Medical Center, Sacramento. Sat.–Sun. Contact: UCD.

October 18—**Los Angeles Society of Plastic Surgeons 19th Annual Symposium.** Los Angeles Society of Plastic Surgeons at Wyndham Bel Age Hotel, West Hollywood. $40–$175. Sat. 6 hrs. Contact: Joanne Cummings (310) 539-6500.

December 12–13—**Annual Advanced Seminar in Urologic Surgery.** UCSF at Ritz-Carlton Hotel San Francisco. Fri.–Sat. 14.5 hrs. Contact: UCSF (415) 476-4251.

GENERAL/MULTIDISCIPLINARY

September 18–21—**8th Annual Conference of The American Academy of Pain Management.** Alexis Park Hotel & Spa, Las Vegas, Nevada. Contact: AAPM, (209) 533-9744; Email: aapm@aapainmanage.org; Website: www.aapainmanage.org.

September 19—**Student Health Connect.** UCSD. Fri. 8.5 hrs. $50. Contact: Sherry Torok (619) 292-2092.

September 19—**Wound Care Symposium.** Long Beach Memorial Medical Center. Fri. 7.5 hrs. $100. Contact: Celia Loney or Don Winant (562) 933-6951.

September 29 & October 6—**ACLS Instructor Course.** AHA at Concord. 10 hrs. Mon. $195. Contact: Rozann (510) 754-7900 or Alice (510) 828-1563.

October 3—**Pre-ACLS Study Workshop.** AHA at San Leandro. Fri. 7.5 hrs. $50–$70. Contact: CPR Seminars (510) 632-6135.

October 11–12—**Cost Effective Evaluation of Functional Capacity.** UCSD at OrthoMed, La Jolla. Sat.–Sun. 14 hrs. $450. Contact: Kerri Kazala (619) 550-7008.

October 16–18—**The Design and Method of Clinical Trials.** UCSF at Laurel Heights Campus. $375. Thurs.–Sat. 12 hrs. Contact: UCSF.

October 22–25—**Wound Management Workshop.** UCSD at La Jolla Marriott. Wed.–Fri. 17 hrs. $475. Contact: Edith Bookstein (619) 454-3212.

October 24—**ACLS Renewal.** AHA at San Francisco. Fri. 6 hrs. $100. Contact: CPR Seminars (510) 632-6135.

October 25–26—**ACLS Provider.** AHA at San Francisco. Fri. 16 hrs. $170. Contact: CPR Seminars (510) 632-6135.

October 23–26—**Nevada Academy of Family Physicians 9th Annual CME/Golf Meeting.** The Orleans Hotel & Casino, Las Vegas. 19 hrs. Contact: Barbara Bolling, NAFP, PO Box 27713, Las Vegas, NV 89126-1713. (702) 228-5822.

October 31–November 3—**Spanish for the Medical Profession.** San Diego. Maricopa Health System. $695. 36 hrs. Contact: Joanna Rios, 1351 E. Ft. Lowell Road, Suite C, Tucson, AZ 85719. (619) 218-4875 or (520) 881-3295.

November 3–6—**Orientation Course in Hyperbaric Medicine.** Long Beach Memorial Medical Center. Mon.–Thurs. 27.5 hrs. $550. Contact: Celia Loney or Don Winant (562) 933-6951.

November 7—**Wound Care Symposium.** Long Beach Memorial Medical Center. Fri. 7.5 hrs. $100. Contact: Celia Loney or Don Winant (562) 933-6951.

December 5–8—**Spanish for the Medical Profession.** Los Angeles. Maricopa Health System. $695. 36 hrs. Contact: Joanna Rios, 1351 E. Ft. Lowell Road, Suite C, Tucson, AZ 85719. (619) 218-4875 or (520) 881-3295.

January 28–31, 1998—**Medicine Meets Virtual Reality:6. Art, Science, Technology: Healthcare (R)Evolution.** San Diego Hyatt Regency. Wed.–Sat. Contact: AMA, Inc. (760) 741-8841.

January 31–February 2, 1998—**Spanish for the Medical Profession.** San Diego. Maricopa Health System. $695. 36 hrs. Contact: Joanna Rios, 1351 E. Ft. Lowell Road, Suite C, Tucson, AZ 85719. (619) 218-4875 or (520) 881-3295.

February 13–16, 1998—**California Academy of Family Physicians 50th Annual Scientific Assembly.** Anaheim Hilton and Towers. $275–$385. 26+ hrs. Contact: Clark W. Franklin, California Academy of Family Physicians, 114 Sansome St., Suite 1305, San Francisco, CA 94104-3824. (415) 394-9121; fax (415) 394-9119; Email: cfranklin@familydocs.org.

HOME STUDY/SELF-ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

The listing of continuing medical education programs in Idaho is compiled by the Ada County Medical Society. To list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701. (208) 336-2930.

Brochures, course information, and registration forms are available from the contact person or organization.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

September 22–26—**MMI Healthcare Risk Management Certificate Program (HRMCP).** Albuquerque Marriott Hotel. Mon.-Fri. Contact: Gail Harris, (505) 883-0266.

October 23-24, 1997 (and half day medical intensives on October 25, 1997)—**Critical Issues in Child & Adolescent Mental Health.** Park City, Utah. Yarrow Convention Center. Contact: ESI Management Group, (801) 272-9446.

January 23–24, 1998—**28th Annual Winter Pediatric Orthopaedic Seminar.** Albuquerque. Fri.-Wed. Contact: UNM Continuing Medical Education, Campus Box 713, Albuquerque, NM 87131-5126. (505) 272-3942, fax (505) 272-8604.

February 25–28, 1998—**Advances in Neurology.** Santa Fe. Contact: UNM Continuing Medical Education, Health Sciences and Services Building, Room 140, Box 713, Albuquerque, NM 87131-5126. (505) 272-3942, fax (505) 272-8604 or e-mail dmurray@unm.edu..

March 20–21, 1998—**Advances in Primary Care.** Albuquerque. Crowne Plaza Hotel. Contact: UNM Continuing Medical Education, Campus Box 713, Albuquerque, NM 87131-5126. (505) 272-3942, fax (505) 272-8604.

SATELLITE COURSES

Immunization Update 1997
September 17

Hepatitis C
Sometime in November

Contact: Joe Treat or Jim Cato, Immunization Program, (505) 827-2366

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.

DM: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.

ETS: Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.

FHP: FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UANS: Utah Association of Neurological Surgeons, 24 S 1100 East, Ste 302, Salt Lake City 84102. (801) 531-7806.

UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

OTHER CME OPPORTUNITIES

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. November 14–16—**Scottsdale Headache Symposium**. Scottsdale at Marriott's Camelback Inn Resort & Spa. Contact: (609) 845-1720.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. January 16–18, 1998—**Headache Now/Cancun**. The Ritz-Carlton, Cancun, Mexico. Contact: (609) 845-1720

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. June 26–28, 1998—**Fortieth Annual Scientific Meeting of The American Association for the Study of Headache**. Sheraton Palace, San Francisco. Contact: (609) 845-1720

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. November 6–8, 1998—**Scottsdale Headache Symposium**. Scottsdale at Marriott's Camelback Inn Resort & Spa. Contact: (609) 845-1720..

AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE. October 26–30—**49th Annual State-of-the-Art Conference**. Opryland Hotel, Nashville, Tennessee. Sun.–Thur. Contact: ACOEM, 55 W. Seegers Rd., Arlington Heights, Ill 60005. (847) 228-6850, ext. 184, FAX (847) 228-1856; Website: www.acoem.org.

AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE. April 24–May 1, 1998—**57th American Occupational Health Conference**. Boston, Mass. Contact: ACOEM, 55 W. Seegers Rd., Arlington Heights, Ill 60005. (847) 228-6850, ext. 184, FAX (847) 228-1856; Website: www.acoem.org.

Arrhythmias: Interpretation, Diagnosis & Management. *July 11–13*, Hyatt Regency, Lake Tahoe, NV. *October 31–November 1*, Le Meridien, San Diego. *December 12–14*, Monte Carlo Hotel, Las Vegas, NV. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

The Atopy Syndrome in the Third Millenium. *October 2–3, 1998*, Zurich, Switzerland, on the occasion of the 50th anniversary of the allergy unit at the Dept of Dermatology, University Hospital, Zurich, and in collaboration with the European Academy of Allergology and Clinical Immunology. Contact: Prof. Dr. B. Wüthrich, Zurich, 41-1-255-3079, fax 41-1-255-4431.

Clinical Endocrinology for Primary Care Physicians. *September 26–28*, Crowne Plaza Hotel, San Francisco, CA. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

Coronary Heart Disease Update. *August 22–24*, Hyatt regency, Monterey, CA. *November 21–23*, Monte Carlo Hotel, Las Vegas, NV. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731

Dermatology for the Non-Dermatologist. *September 26–28*, Monte Carlo Hotel, Las Vegas, NV. *November 21–23*, Disneyland Pacific Hotel, Anaheim, CA. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

Managing Respiratory Diseases. *August 8–10*, Tenaya Lodge, Yosemite, CA. *October 31–November 2*, The Phoenician Resort, Scottsdale, AZ. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

Neurology for the Non-Neurologist. *August 8–10*, Snowmass Lodge, Aspen, CO. *October 24–26*, Monte Carlo Hotel, Las Vegas, NV. *December 12–14*, Camelback Inn, Scottsdale, AZ. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

UNIVERSITY OF NEBRASKA. September 22–27—**Skills and Knowledge for the Practicing Physician**. Omaha. Mon.–Sat. $750. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. October 6–8—**5th International Symposium "Blood Cell Transplantation."** Omaha. Mon.–Wed. $350. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. October 10—**5th Annual College of Medicine Alumni Day**. Omaha. Fri. Free. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. December 11–13—**Obstetrics & Gynecology Conference**. Bally's, Las Vegas, NV. Thu.-Sat. $325. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha NE 68198-5651. (800) 642-1095.

Articles

Overcoming Social and Cultural Barriers To Care for Patients With Diabetes

JOSEPH HUMPHRY, MD, FACP; LOLANI M. JAMESON, MPH; *and* SHEILA BECKHAM, RD, MPH, CDE, *Waianae, Hawaii*

We attempted to develop a culturally sensitive alternative approach to diabetes management in a multiethnic, socially disadvantaged community (Waianae, Hawaii). The aims of this 3.5-year demonstration project were to establish regular community-based medical contact with diabetic patients who had a history of nonadherence to treatment regimens and to determine whether this strategy would lead to better health care (particularly improved self-management) in these patients. This community-based, culturally sensitive outreach system of medical follow up dramatically improved the amount and quality of medical care provided to this high-risk subpopulation of patients with diabetes.

(Humphry J, Jameson LM, Beckham S. Overcoming social and cultural barriers to care for patients with diabetes. West J Med 1997; 167 September:138–144)

Managed care has focused attention on populations at high risk for adverse outcomes or excessive costs. Patients with diabetes consume two to two-and-a-half times more health care dollars than the average person. This population accounts for approximately 15% of the total cost of health care ($90 billion dollars annually) in the United States.[1] In addition, a subpopulation of patients with diabetes fails to seek regular care or adhere to recommended care plans, thus increasing their risk of suffering acute and chronic complications. As is to be expected, patients who fail to seek regular follow-up care often have poor metabolic control and lack the skills necessary to manage their disease.[2]

Results of the Diabetes Control and Complications Trial show that improved metabolic control substantially reduces the rate of microvascular complications in patients with type 1 diabetes.[3] The recent medical literature also strongly supports the benefits of improved metabolic control for patients with type 2 diabetes.[4–7] It is imperative to develop methods for improving metabolic control. Most therapeutic interventions have been developed in academic or diabetic centers and do not include patients who do not seek medical care or who fail to follow medical recommendations. Recognition of the greater burden of diabetes in minority populations[8] has focused attention on the failure of the health care system to address the unique needs of certain groups.[9] Table 1 lists barriers that play a role in the high rates of noncompliance among minorities.

Primary care physicians are directly involved in the care of 90 to 95% of patients with diabetes,[10] but they lack many of the resources and skills required to implement programs of diabetes education and self-management. In this article, we describe the results of a 3.5-year demonstration project using community health care workers as primary providers for a subpopulation of minority patients with diabetes who repeatedly failed to comply with regular medical regimens.

Methods

Setting

The Waianae Coast Comprehensive Health Center (WCCHC) is a community-owned and -operated health center with 400 employees who provide medical and support services in a community of more than 40,000 people. The WCCHC is a primary care multispecialty group practice that features a free-standing emergency room, nutrition/preventive care, and home health, behavioral health, and transportation services. Approximately one-half of the Waianae population uses the WCCHC as their principle source of primary health care. The ethnic composition of the community is predominantly Native Hawaiian or part Hawaiian (48%), with 24% Caucasians, 11% Asian-Pacific Islanders, 9% Filipinos, and 8% others. This facility provided the setting for the Diabetes Prevention Project.

From the Waianae Coast Comprehensive Health Center, Waianae, Hawaii.
Reprint requests to Joseph Humphry, MD, FACP, 86-260 Farrington Hwy, Waianae, HI 96892-3199.

ABBREVIATIONS USED IN TEXT
WCCHC = Waianae Coast Comprehensive Health Center

Project Design

The Diabetes Intervention Project was undertaken to provide a culturally sensitive, community-based alternative to the mainstream health care system in the management of diabetes. The primary objective of the project was to establish regular medical contact with patients who suffered from diabetes and who repeatedly failed to improve under the office-based medical care system. The secondary objective was to measure the impact of establishing regular contact with health care workers on metabolic control in these patients. An advisory coalition composed of health care agencies and community groups was actively involved in the project development and implementation. The project coordinated several ongoing diabetes-related activities at the WCCHC. This report focuses on the design, implementation, and impact on a local subpopulation of diabetic patients of a health care system centered on community health care workers.

The community health care workers were medical assistants or paraprofessionals with some medical background and limited formal training. The formal training consisted of a 12-week college-level curriculum in medical assessment, intervention, and case management; a 4-week clinical preceptorship working in with physicians, nurse practitioners, nutritionists, and a certified diabetic educator; and a 4-week community-based training course that involved shadowing a public health nurse. Ongoing continuing education was provided by the certified diabetes educator on a monthly basis.

The existing diabetes team at WCCHC, composed of the physician, nutritionist, certified diabetes educator, health educator, and community health worker, collaborated with public health nursing. The diabetes team functioned as a resource for the community health care workers and patients. The community health care worker's tasks were to establish regular patient contact at home or in the community setting and to develop care management plans in collaboration with the patient and the diabetes team.

Patient selection was based on a repeated pattern of missed appointments with professional health care workers with resultant poor metabolic control or a diagnosis of diabetes in pregnant women or children potentially requiring insulin. Referrals were accepted from all primary care physicians and public health nurses. Patients who met the entrance criteria were informed by their primary care physician of this alternative approach to diabetes care. Patients who consented to participate were referred to the project and assigned to a community health care worker.

The community health care worker became the principle coordinator of health services for the patient. Each

Table 1.—*Obstacles to Effective Diabetes Management*

Transportation	In rural communities, there is limited public transportation, and many families have no regular daytime car available by which to reach medical care facilities. There is also a significant reliance on others. It is not uncommon to have people charge for providing a ride to the doctor.
Culture	In a multiethnic community, many people have beliefs about health that influence their behavior both in health and in sickness. Western medicine has an involved and complicated system requiring multiple bureaucratic procedures to receive care. Providers may not be culturally sensitive and may attempt to impose attitudes or behavioral changes not welcomed by the patient. In providing care for some non-Western subpopulations, a more personal, trusting relationship is vital.
Family	Health is a family responsibility in some cultures. Health care (for example, insulin injections and medically relevant decisions) is provided by one or more family members who are rarely available in the office setting. The patient's need to provide care to other family members can often influence the attention given to their own health needs.
Economics	The cost of medical care for patients with chronic illnesses extends far beyond the cost of direct services. Such patients may require special food, exercise, transportation, and other comprehensive services to effectively manage their diabetes. Usually, these costs are not included in health insurance plans, leaving insufficient resources to achieve effective diabetes management and control.
Limited Access	Chronic disease management requires access to effective medical education as well as medical treatment. In the primary care setting, a team approach is rarely used, many communities having neither a chronic disease expert or nutritionist available.
Denial	Even with a full understanding of diabetes, some patients may choose to ignore the disease and live with mild symptoms. Avoidance of long-term complications may not be a sufficiently rewarding prospect with which to encourage these patients to make major life changes.
Social Issues	Families often have other major priorities that detract from or disrupt long-term chronic disease management. These crises can be either acute or chronic, but need some resolution before disease management can become a priority for the patient and his or her family.
Multiple Medical Problems	Often medical therapies and priorities are confusing for patients with multiple medical problems. Diabetes management is also difficult in patients with chronic mental illness or intellectual impairment.

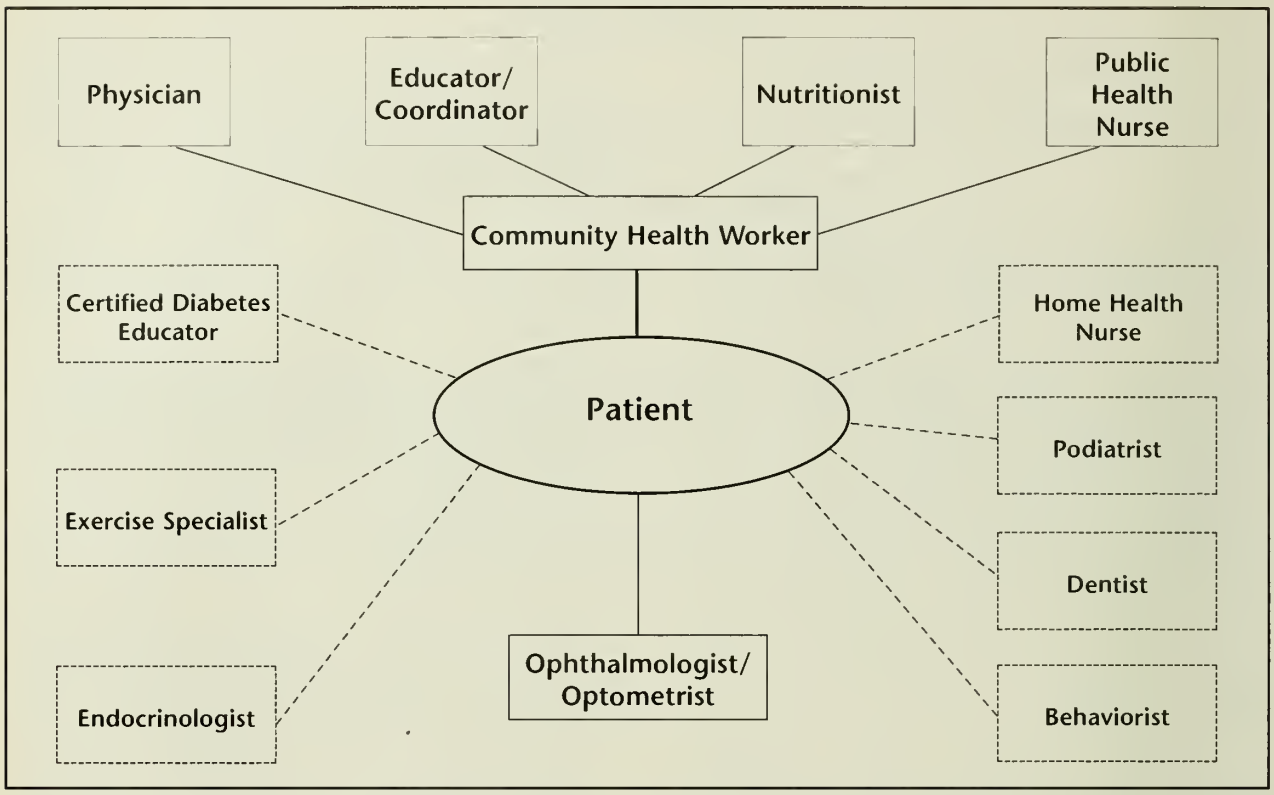

Figure 1.—Team organization of the Ohana Health Outreach Program. —, mandatory team members; - - -, optional team members.

patient was fully informed of the scope of the project and had direct access to all members of the diabetes team, but was under no obligation to have medical contact with anyone besides the assigned worker. Patients also had the option of continuing to receive community-based follow-up care. There was no effort to return the patient to office-based care or set a time limit on these community-based services.

Weekly case conferences were held that included all members of the diabetes team except the physician director. Patients were included in these meetings if they wished. All cases were reviewed on a regular basis, and other team members were updated on each patient's status. Patients were scheduled for visits based on their condition and treatment plan. New and unstable patients were also discussed and treatment plans were developed for them by the team. These patients were seen at least once a week, whereas more long-term or stable patients were seen at least once a month.

Attending physicians were contacted for changes in patient status or medical regimen. The physician director was available at any time via beeper and cellular telephone for acute situations in which the attending physician was not immediately available. The community health care workers' progress notes were entered into the patients' charts and routed to the primary physicians for review.

As the primary contacts for the health care system serving this select patient population, the community health care workers, in conjunction with the diabetes team, were expected to provide a wide spectrum of services (Figure 1). Because most patients were not initially prepared to assume full responsibility for self-management, insulin and other medications were adjusted with the active participation of the patient and physician. This activity was viewed as "co-self-management" in that the community health care worker interacted with both patient and physician to adjust medication in a timely manner, similar to the way motivated patients adjust insulin and other medications in consultation with their physicians through home monitoring. Nutrition and diabetes education were also frequently provided by the community health care workers with the advice of the appropriate team members.

Substantial time was spent in case management to solve either individual or family problems that presented barriers to care. In complicated cases, public health nurses made joint visits with community health care workers if their presence was acceptable to the patients. It was expected that the community health care worker would attempt early in the process to establish a positive relationship with the patient and address potential obstacles to care. Often there were many visits before diabetes management became the focus of attention.

The WCCHC computer system was enhanced to capture data on blood glucose levels, blood pressure, and weight in all patients with diabetes. Data analysis averaged the first two blood glucose and blood pressure read-

Table 2.—*Patient Improvement in Blood Glucose Control After Participation in the Ohana Health Outreach Program (n = 52)*

	Blood Glucose Control		
	Good	Fair	Poor
Initial	13 (25%)	19 (37%)	20 (38%)
Final	18 (35%)	24 (46%)	10 (19%)

ings and compared these with the previous two averaged readings. The patients' most recently recorded weight was compared with their initial weight. Because this was a demonstration project and because of limited funds, the project did not focus on data collection and analysis; thus the results are reported without statistical evaluation.

Results

Demographics

Ninety-four patients took part in the project and were tracked from January 1991 until March 1995. Data on 52 nonpregnant adults were accumulated by community health care workers and physicians, both before and during the intervention. The average patient was followed for 2.9 years (range 0.4–4.2 years). One patient was followed for less than 1 year, whereas a majority of the patients were followed for more than 2 years. On average, the patients had a total of 63 encounters with health care workers (range 13–170 encounters) or 2.2 encounters per month. Nineteen patients were discharged before the scheduled termination of the project for the following reasons: six patients died, six moved out of the area, two changed health plans, one was started on dialysis, three refused further services, and one was discharged out of concern for the community health care worker's safety. Of the remaining 75 patients, 56 were female and 19 were male, with the following age ranges: newborn to 20 years, seven patients; 21 to 30 years, 20 patients; 31 to 40 years, nine patients; 41 to 60 years, 26 patients; and older than 60 years, 13 patients. The ethnic composition of the patient population was as follows: 61% Native Hawaiian/part Hawaiian, 11% Samoan, 11% Caucasian, 9% Filipino, 4% Japanese, and 4% Hispanic.

Services were also provided to 18 pregnant patients, two of whom became pregnant during the study and are included twice in the total count.

Nonpregnant Adults

The 52 nonpregnant adults in the project lost an average of 5.4 pounds each. The changes in weight varied substantially, with seven (13%) losing 25 pounds or more and 19 (37%) experiencing a 10- to 24-pound loss. On the other hand, 11 participants (21%) gained 10 pounds or more.

The average decrease in blood glucose among the project participants was 49.8 mg/dl. Applying criteria developed by the Indian Health Service, the initial and final random blood glucose levels were analyzed and categorized as follows, based on the level of blood sugar control: good (blood glucose <165), fair (>165 and <250), or poor (>250) (Table 2). Twenty-one participants (40%) improved blood glucose control (average change in blood glucose –117 mg/dl), 21 (40%) remained the same (average change in blood glucose –6 mg/dl), and 10 (20%) saw a decline in control by the end of the demonstration project (average change in blood glucose +99 mg/dl).

Seventeen of these patients initially had hypertension (blood pressure >140/90). The average systolic drop in blood pressure was 20.5 mmHg (range –5.0 to –57 mmHg) by the end of the project. Diastolic blood pressure drop averaged 6.1 mmHg (range +19 to –20.5 mmHg).

Table 3.—*Conditions of Pregnant Women Who Took Part in the Ohana Health Outreach Program*

Condition	Percentage of Patients (n)
Pregestational diabetes mellitus (presumed)	66 (12/18)
Required Insulin	94 (17/18)
Preterm Hospitalization	18 (3/16)
Cesarean Section	56 (9/16)
Premature Delivery	12 (2/12)
Macrosomia (weight >4,500 g)	6 (1/16)

Diabetes and Pregnancy

The project co-managed 18 pregnant women with diabetes during the study period: two were 16 years old, eight were between 21 and 25, six were between 26 and 30, and two were older than 30. Twelve women presented with pregestational diabetes or a first trimester blood glucose elevation consistent with pregestational diabetes requiring insulin therapy at the time of presentation (Table 3). All but one of the cases required insulin therapy during the pregnancy. None of the women achieved pregestational diabetes control; in addition, two continued to smoke throughout gestation despite intense counseling, and at least one continued to use methamphetamines during pregnancy. Three women required preterm hospitalizations, and one patient with twins had a prolonged hospital stay as well as two short stays for treatment of premature contractions.

Nine women delivered by C-sections, seven delivered vaginally, and two moved out of the area prior to delivery. Of the two infants delivered prior to 36 weeks' gestation, one weighed less than 2500 g and the other more than 4500 g. There were no delivery-related complications. HbA_{1c} specimens were not routinely obtained during the study period, which limited our ability to assess the level of metabolic control.

Patient Satisfaction Survey

In 1994, an independent evaluator conducted a patient satisfaction survey. Forty-three patients met the criteria of

Table 4.—Ethnic Affiliation of Patients in the Ohana Health Outreach Program

Ethnic Affiliation	Proportion of Waianae Community (%)	Proportion Participating in Project (%)
Hawaiian/Part Hawaiian	48	61
Caucasian	24	11
Asian/Pacific Islander	11	15
Filipino	9	9
Other	8	4

either being in the project for more than 1 year or receiving 20 or more visits from community health care workers. Of these patients, 24 were interviewed, one refused to be interviewed, five failed three times to show up for the interview, and 13 were lost to follow up. The patient satisfaction survey featured a series of questions assessing the patient's attitude toward the quality of health care delivery by the community health care worker using a subjective rating scale. Eighty-three percent of the patients were "always" satisfied with the care provided by the community health care workers. A response of "sometimes" was reported 9% of the time, whereas only 1% rated the care as "never" satisfying (7% responded "don't know"). In general, 54% were reportedly "always" satisfied with the project in general, 14% were "sometimes" satisfied, and 7% replied that they were "never" satisfied with the project (8% replied "don't know").

Discussion

A significant percentage of patients with chronic disease fail to consistently seek medical care or comply with recommended treatment regimens. Because of a variety of obstacles, the current office-based health care system is not capable of effectively addressing the needs of many patients with chronic diseases.[11] To improve care for a subpopulation of patients with diabetes, alternative approaches to management need to be developed and evaluated. The Diabetes Intervention Project provides a viable means of improving health care for a select group of patients who fail to control their diabetes using the mainstream health care system.

The patients referred to the project formed a diverse group. Many participants were young, relatively healthy, and asymptomatic and elected not to make treatment of their disease a high priority. Another group was older and chronically disabled, with longstanding resistance to care, despite suffering from diabetic complications and multiple diseases. Several patients had major chronic psychiatric disorders or suffered from mental impairment. All children and adolescents with diabetes at the WCCHC were referred to the project.

The first objective of the project was to establish regular medical contact with previously nonadherent diabetic patients. The project was remarkably successful at improving regular contact between the patient and one or more team members. Patients had contact an average of 2.2 times per month in addition to regularly scheduled contact from the community health care workers. By offering the convenience of home- and community-based medical follow-up and placing the responsibility for a minimum of monthly contact with the community health care workers, the project succeeded in providing nonadherent patients with regular medical care. Only three of the 19 patients who were discharged from the project requested that the service be discontinued; the others were discharged because of death or other external factors. The majority of the participants belonged to ethnic minorities (Table 4). The project provided service to an increased percentage of Hawaiians and Samoans and a decreased service to Caucasians compared with the total population of the Waianae community.

The second objective of the project was to test whether this approach would result in improved diabetes management as measured by blood glucose, weight, and hypertension control. The physiologic results show clear improvement in all parameters for the total population. Despite the challenging clientele, 19 (37%) of the 52 nonpregnant patients lost 10 pounds or more. This success was partially accounted for by the integration of the project with the Waianae Diet Program, a culturally-sensitive, 3-week program stressing traditional foods and values.[12,13] Even when patients did not participate in the Waianae Diet Program, the strong support of the nutritionist was clearly evident in the outcomes.

The total adult population, excluding pregnant women, showed an average drop in blood glucose of nearly 50 mg/dl. This success was not shared by all the participants; 40% of these adults attained the highest decrease in average blood glucose. These 52 patients were a diverse group with respect to age, concurrent diseases, ethnicity, and social situation; this diversity prevented us from ascertaining the characteristics of the group that enjoyed the greatest improvement in diabetes control as measured by reductions in blood glucose levels. Informal review of the group of patients who required the most frequent interventions and who often showed the least successful outcomes indicated that these patients often had major illness in addition to diabetes; furthermore, their conditions were often complicated by major psychiatric or social problems. In pregnant patients who went on to deliver children, there also appeared to be a postpartum period lasting up to 6 months during which they were unable to focus on adequate management of their diabetes.

The pregnant diabetic patients presented a formidable challenge. The unusually young average age of these patients is in part a reflection of the increasing prevalence of type 2 diabetes in younger members of certain minority populations. The intensive insulin therapy required to achieve acceptable blood glucose control in these patients demands resources beyond the capacity of most rural practitioners. The availability of community and home-based teaching and management markedly

improved the patients' compliance and blood glucose control over our previous office-based team approach.

The community health care worker was the cultural expert who linked the nonadherent patient with the health care professionals on the project team. Bonding between the patient and the community health care worker was critical in establishing positive relationships with the health care system and ultimately promoting self-management. This bonding was facilitated by selecting community health care workers who were culturally sensitive and lived in the community; it was further encouraged in that the community health care workers spent up to 2 hours on the initial visit, worked according to a flexible schedule, and promoted a family-centered approach by frequently assisting other family members besides the diabetic patient. In several cultures in the Waianae area, a family member takes primary responsibility for another member with chronic disease. The community health care workers were excellent at understanding and working with these key family members to improve patients' diabetes management. The patient satisfaction survey confirms the effectiveness of this bonding, as do the subsequent changes in patient behavior leading to metabolic improvement.

In general, the project complemented the mainstream health care system. Early detection of problems, coordination of care, and timely physician visits promoted effective medical intervention. Most patients preferred to have regular follow-up with the community health care workers with infrequent medical contact as long as they were continuing with effective self-management. There was an increase in the total number of professional visits made by this patient population during the study period, reflecting the fact that most of these patients had limited prior contact with health care professionals. The visits were no longer prompted by acute crisis, but were orchestrated with the community health care worker to reach disease management goals. Although resource consumption was not monitored, there were numerous occasions on which the community health care worker and the diabetes team were able to intervene during the early stage of an acute illness, avoiding hospitalization and more costly care.

The role of community health care workers in our project was unique compared with most other programs using outreach workers in that our community health care workers provided direct service. The project's community health care workers performed and were involved in supervising and encouraging complex medical and educational tasks. The project was patient-centered, targeting and promoting patient empowerment and improved self-management. The community health care worker assumed responsibility as the case manager by gathering information, contacting the appropriate professional member of the team, deciding on a course of action in conjunction with the patient and professional, and providing support and education for patient-centered implementation of the care plan. The community health care worker provided interventions targeting a variety of infectious and chronic conditions for the patients and their families. The case load varied in intensity and complexity, although virtually all patients encountered major obstacles to effective self-management. The benefits of the approach demonstrated by our projecdt are best appreciated by individual examples. What follows are two brief case reports of patients whose care was significantly enhanced through the efforts of the community health care workers:

1. FT, a 39-year-old, morbidly obese (322 lbs) Samoan man with mild mental retardation and limited English skills, was initially hospitalized with acute gout, severe obstructive sleep apnea, secondary right-ventricle heart failure, severe hypertension (220/140), and newly diagnosed diabetes. After he was referred to the project, the community health care worker established regular contact with him and obtained his compliance with a complex medication regimen (including nasal C-PAP through a weekly pill box) by means of constant positive reinforcement. Close work with the family allowed a family-based daily exercise routine and subsequent marked improvement in the patient's multiple medical problems.
2. SK, a 16-year-old Hawaiian girl with IDDM diagnosed at age 5, was referred to the project after reestablishing medical care at WCCHC in her 12th week of pregnancy. She was single, from a broken home, well known to public health nursing, and already enrolled in a special class for pregnant students. Her last recorded HbA_{1c} was 20.7, reflecting chronic nonadherence to diet and blood glucose monitoring. With the involvement of a community health care worker, she was placed on an insulin regimen of four injections per day following an adjustable schedule. The patient monitored her blood sugar four to six times per day and substantially improved in dietary compliance. At 38 weeks' gestation, she had gained 30 pounds, presented with a HbA_{1c} level of 7.2, and delivered a normal-weight infant.

Limitations of the Project

An obvious drawback to using community health care workers as the primary providers of care is their relative lack of professional training and expertise. These workers were acutely aware of their limited medical knowledge. Assuming this level of responsibility challenged them and, at times, became problematic. There were occasions when patients were given incomplete or inaccurate information, particularly early in the workers' training. Sometimes they did not respond immediately to abnormal blood pressure or blood glucose readings, deferring intervention until after case conference or direct contact with the physicians. This pattern of care delayed appropriate intervention initially, but improved with time and training. Over time, the community health care workers become more comfortable as members of the team and became more familiar with the specific criteria that called for making a change in their patients'

care plans. The diabetes team progressively developed policies and procedures, refining the project and structuring guidance for the community health care workers and other team members, although at no time were medications changed without direct contact with the physician.

A second, more specific weakness that came to light during the course of the project was the community health care workers' lack of preparation in training and counseling related to death and dying. For weeks or months at a time, these workers were often the only health care professionals to have contact with patients having complex medical problems. Because of the design of the project, the community health care workers became very close to their patients and felt a deep sense of responsibility regarding their well-being. When a patient died, the workers experienced intense feelings of failure and guilt even though the death was clearly from progressive complications usually related to large-vessel cardiovascular disease. The professional team provided support and training for the community health care workers in managing the emotional burdens of caring for severely and terminally ill patients.

The project was designed to test whether a community-based program of care would improve patient compliance with regimens for managing diabetes. Although information was gathered, the project intentionally did not stress data collection or metabolic control, focusing instead on sustained patient contact. As a preliminary study of this approach, the data that were collected clearly support the value of this alternative to the office-based care model. Further research is needed to better quantify the metabolic impact and determine whether this approach is effective in other communities.

As with most chronic diseases, diabetes requires major behavioral changes to bring about improved metabolic control. Equal to the need for quality medical management is the need for a health care delivery system that promotes sustained, culturally sensitive care. We believe that the partnership between the professional diabetes team and the community health care workers in delivering community-based care provides an effective model that merits further research and development. In the evolving managed care environment, quality care needs to be available to the largest possible proportion of the population, sometimes through unique approaches to address the numerous obstacles to effective care.

Acknowledgment

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Articles

Rapid Hospital Discharge Following Laparoscopy For Ectopic Pregnancy

A Promise Unfulfilled?

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This study was done to determine whether laparoscopy for ectopic pregnancy in the United States is associated with rapid postoperative discharge, defined as 2 days or less, and to estimate how often ambulatory treatment of ectopic pregnancy occurs without subsequent hospital admission. We used the National Hospital Discharge Survey to estimate the frequency of ectopic pregnancy admissions, operations, and length of hospital stays in 1990. We used the National Ambulatory Medical Care Survey to estimate the number, type, and disposition of office visits for ectopic pregnancy in 1990. According to National Hospital Discharge Survey data, tubal pregnancy led to an estimated 57,000 hospital admissions in 1990. Most (70%) of the 26,000 patients treated with laparoscopy were in the hospital 3 days or more, and most (73%) underwent salpingectomy. The number of ambulatory visits for ectopic pregnancy was too low to estimate reliably according to the standards of the National Center for Health Statistics. We found that laparoscopy was used frequently for the treatment of ectopic pregnancy but was not associated with rapid postoperative discharge. Further research is needed to determine whether these findings persist and whether reimbursement incentives, patient preference, or problems with the diffusion of technology are responsible.

(Learman LA, Grimes DA. Rapid hospital discharge following laparoscopy for ectopic pregnancy: a promise unfulfilled? West J Med 1997 September; 167:145–148)

Ectopic pregnancy is epidemic in the United States: from 1970 to 1987, the number of ectopic pregnancies in the United States increased fivefold to 88,000, and the rate increased from 4.5 to 16.8 per 1000 pregnancies.[1] During the same period, the case-fatality rate declined, owing primarily to improved diagnosis before tubal rupture and hemorrhage. Earlier diagnosis has increased the number of patients eligible for treatment by laparoscopy and methotrexate regimens.

Proponents of the use of laparoscopy for ectopic pregnancy can cite a number of case-control studies, prospective cohort studies, and a randomized controlled trial reporting more rapid hospital discharge following laparoscopy and the same operating time compared with laparotomy.[2–6] In a "technology assessment" article, it was concluded that doing routine laparoscopy for ectopic pregnancy would have saved third-party payers more than $100 million in direct hospitalization costs in 1987 compared with the use of laparotomy.[7] The authors based their estimate of hospitalization costs on a single, small randomized controlled trial in which the average length of hospital stay was 1.4 days for laparoscopy and 3.3 days for laparotomy.[6]

To evaluate the length of hospital stay for ectopic pregnancies treated with laparoscopy, a representative sample of US practitioners and hospitals is required. The "effectiveness,"[8] or real-world use, of laparoscopy may vary markedly from estimates being used in cost-effectiveness analyses.[7,9] As shown by the National Center for Health Statistics (NCHS) in 1981,[10] the switch from laparotomy to laparoscopy for tubal sterilization dramatically reduced hospital stays in the 1970s. We conducted this study to determine whether laparoscopy treatment of ectopic pregnancy has had a similar effect on US hospital use. Using data from the NCHS, we evaluated whether the use of laparoscopy for treating ectopic pregnancy was associated with hospital stays of two days or less. We also attempted to estimate how often ectopic pregnancy was treated in the outpatient setting without subsequent hospital admissions.

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ABBREVIATIONS USED IN TEXT

CI = confidence interval
ICD9-CM = International Classification of Diseases, 9th Revision, Clinical Modification
NAMCS = National Ambulatory Medical Care Survey
NCHS = National Center for Health Statistics
NHDS = National Hospital Discharge Survey
OR = odds ratio

Patients and Methods

This study describes ectopic pregnancy hospital admissions, procedures, and office visits in the United States in 1990. The NCHS conducts the National Hospital Discharge Survey (NHDS) annually to provide a population estimate of hospital use in the United States. The NHDS is a national probability sample of inpatient admissions to general and short-stay hospitals, excluding federal, military, and Veterans Affairs hospitals. The NHDS sample is stratified by geographic region and number of hospital beds. It samples ambulatory surgery centers based at short-stay hospitals, but it does not sample free-standing ambulatory surgery centers in the United States.[11]

In 1990 the NHDS included data from 474 (91.3%) of the 519 acute care hospitals in the United States within the scope of the survey. When the 235,947 discharge records in the 1990 NHDS are statistically weighted to adjust for the likelihood of being sampled, they provide an estimate of the demographic, diagnostic, and procedural data for 30,787,939 US hospital discharges. In the NHDS database, as many as seven diagnoses and four procedures are abstracted from discharge records and encoded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD9-CM).[11]

The NCHS conducts the National Ambulatory Medical Care Survey (NAMCS) annually to describe the use of ambulatory medical services in the United States. The NAMCS uses a multistage sampling design stratified by geographic region, practices within regions, and patient visits within practices. In 1990, the survey included 43,469 visits sampled from 1,684 physicians, comprising 0.5% of physicians practicing in the United States. When the sampled visits are statistically weighted to adjust for the likelihood of being sampled, they provide an estimate of the demographic, diagnostic, and procedural data for 704,603,932 estimated visits made by all patients in the United States in 1990. The rate of sampling varied from 100% of visits to small practices to 20% of visits to the largest practices. Patient visits are weighted using similar methods as for the NHDS to provide national estimates of ambulatory care use. In the NAMCS database, as many as three diagnoses per visit are recorded using ICD9-CM codes. The survey includes data on outpatient treatments, including ambulatory surgery, which is defined as "any surgical procedure performed in the office or ordered to be performed elsewhere on an outpatient basis." Patient disposition data include the decision "Admit to hospital," for which the instructions read "Patient is instructed that further care or treatment will be provided in a hospital. No further office visits are expected before that decision."[12]

We performed a detailed analysis of 1990 NHDS data files published in CD-ROM formats.[13] We first created a subset of files that included only discharges with the diagnosis of tubal pregnancy (ICD9-CM code 633.1). We then determined the number of patients in the subgroup who were discharged following partial or complete salpingectomy with or without oophorectomy (ICD9-CM codes 65.4, 66.4, 66.5, 66.62, and 66.69) and the number discharged following salpingostomy or salpingotomy (ICD9-CM code 66.01 and 66.02). In an effort to identify the surgical approach used, we determined how many discharges included a procedure code for laparoscopy (ICD9-CM code 54.21) and laparotomy (ICD9-CM codes 54.11, 54.19). We expanded 1990 sample data into US population estimates using weights and computer software developed by the NHCS and included in the NHDS database. We calculated relative standard errors for aggregate estimates using constants and formulas published by the NCHS.[11] We followed the NCHS guidelines for presenting only estimates based on adequate sample sizes and relative standard errors of less than 30%.

We used NAMCS data files published in CD-ROM format[13] to estimate the number of office visits for ectopic pregnancy (ICD9-CM code 633) in 1990. We then excluded visits for postoperative care using diagnostic codes and visit reason codes. For remaining visits, we calculated the proportion followed by hospital admission or by ambulatory surgery. In 1990, office visits numbering less than 300,000 had relative standard errors of more than 30% and, according to NHCS guidelines, should not be used as an accurate reflection of national ambulatory care use.

Results

Of the estimated 65,000 discharges associated with ectopic pregnancy in 1990, 56,721 had a specific diagnostic code for tubal pregnancy. Most patients with tubal pregnancy (62%) were 25 to 34 years old, with the remainder evenly distributed in the younger (15 to 24) and older (35 to 44) age groups. In all, 56% of patients with tubal pregnancy were white, and 21% were black. The NHDS did not include a racial or ethnic category for Latina or Hispanic women. Although most patients with tubal pregnancy had private insurance (60%), a substantial minority (17%) were publicly insured (Table 1).

The surgical approach for managing tubal pregnancy was identified in 29,713 cases (53%), with 25,968 cases involving a laparoscope (46%), and 6% of these cases culminating in laparotomy. Because "laparotomy" appeared uncommonly as a listed procedure, we could not reliably estimate the exact frequency of this approach. Most patients underwent salpingectomy, irrespective of the surgical approach used (Table 1). Fewer than 10% of operations involved salpingostomy or salpingotomy.

Relatively more patients having laparoscopy were discharged within 1 day, but most patients (70%) stayed

TABLE 1.—*Characteristics of Patients Admitted to Hospital With Tubal Pregnancy, 1990*

Characteristic	*All Patients, %*	*Laparascapy Group, %*
Age, years		
15 to 24	20	20
25 to 34	62	64
35 to 44	18	16
Race		
White	56	67
Black	21	14
Other or not stated	23	19
Primary source of payment		
Medicaid, Medicare, government sources	17	18
Commercial insurance	60	66
Other or not stated	23	16
Length of stay, days		
≤1	13	20
2	16	10
3 to 4	52	57
≥5	18	13
Tubal procedure performed		
Salpingectomy	74	73
Salpingostomy, salpingotomy	6	8
Other or no procedure	20	19

in the hospital for 3 days or more irrespective of the surgical approach used. Privately insured patients undergoing laparoscopy were more likely than publicly insured patients to be discharged within two days of admission (33% vs 24%; odds ratio [OR] 1.6, 95% confidence interval [CI] 1.5 to 1.7). We found the same difference when comparing white and black patients (27% vs 15%; OR 2.1, 95% CI 1.9 to 2.3).

The 1990 NAMCS was not able to produce a reliable estimate of outpatient visits for the diagnosis and treatment of ectopic pregnancy. Visits were estimated to number 70,141 with a relative standard error of more than 50%, which falls above the National Center for Health Statistics threshold of 30% for considering estimates to be reliable.

Discussion

The switch from laparotomy to laparoscopy dramatically reduced US hospital stays for tubal sterilization in the 1970s.[10] Surprisingly, most patients undergoing laparoscopy for ectopic pregnancy in 1990 stayed in the hospital more than two days. Fee-for-service incentives, patient preferences, and provider habits may be contributing to the problem of prolonged hospital stays following laparoscopy for ectopic pregnancy.

Hospitals and clinicians working in managed care plans have incentives to minimize hospital stays, in contrast with the incentives of fee-for-service plans. In the 1980s the economic burden of ectopic pregnancy started changing from private to public pay sources.[14] Further research is needed to determine why public pay and black patients stayed in the hospital longer following laparoscopy than privately insured and white patients, respectively. These differences may be related to the severity of illness at the time of presentation or to the higher saturation of managed care plans in the private versus public sector hospitals. Whether length of stay will decline as more direct costs of ectopic pregnancy are borne by managed care organizations remains to be seen.

Patients recovering from an unexpected and urgent operation to end a desired pregnancy are unlikely to prefer early hospital discharge, and clinicians may accede to their wishes for an extra day or two. Physicians who earlier in their careers performed laparotomies routinely for ectopic pregnancy may have incorporated laparoscopy into their practices without incorporating expeditious discharge policies. They may view their patients as medically unstable and at risk of bleeding even after surgical treatment.

Despite suggestions to the contrary,[15] there has not been a shift nationwide from salpingectomy to salpingostomy in the surgical management of ectopic pregnancy. The infrequent use of salpingostomy found in our study may be rooted in the lack of skill in performing this procedure (a "diffusion of technology" problem) or rooted in the belief that salpingectomy is a better, more definitive, and more cost-effective option. In 1990 the average practicing gynecologist may have felt more comfortable diagnosing an ectopic pregnancy by laparoscopy than with the specific methods of laparoscopic salpingostomy. In one study testing knowledge of the laparoscopic sterilization techniques, residents were more knowledgeable than practicing gynecologists.[16] If we extrapolate to the more complex procedure of salpingostomy and the removal of tubal contents, clinicians may have been more comfortable selecting a straightforward procedure like salpingectomy.

Gynecologic laparoscopists who are skilled at more than one method of treating ectopic pregnancy may think that salpingectomy is a more definitive and cost-effective procedure. Salpingostomy is followed by at least several blood tests to confirm an appropriate rate of decline in the serum levels of human chorionic gonadotropin. The risk of persistent ectopic pregnancy increases the expense and decreases the effectiveness of the procedure. No randomized controlled trials have compared fertility rates following salpingostomy and salpingectomy, but some investigators have argued that the status of the contralateral tube may be more important than preserving the involved tube.[15]

Our analysis is limited by a lack of data on the outpatient treatment of ectopic pregnancy. Using the best available data from the NCHS, we could not reliably estimate the number of cases diagnosed in physicians' offices. Most of the patients in such cases are admitted

to surgical centers in short-stay hospitals and are represented in the NHDS. We could not determine the fate of patients not admitted to hospitals. We could not predict how many patients received successful methotrexate therapy as outpatients and how many were treated in free-standing surgical centers. As summarized in a recent review article, reports of methotrexate treatment for ectopic pregnancy increased progressively from 8 cases reported in 1983 to 400 cumulative cases by 1993.[17] Cost-effectiveness studies favor medical over surgical treatment.[18] No reports exist that evaluate the safety of surgery for ectopic pregnancy in free-standing surgical units. A recent cohort study describing more than 6,700 assisted reproductive technology procedures in an ambulatory surgical center reported the need for hospital admission in less than 1% of cases,[19] but surgery for ectopic pregnancy differs from assisted reproductive technology procedures in urgency, complexity, and likelihood of hemodynamic instability.

Among patients with ectopic pregnancy treated in US acute care hospitals in 1990, laparoscopy was not followed by the rapid hospital discharge reported in efficacy studies. A gap exists between the benefit of laparoscopy suggested by the results of comparative trials and its real-world effectiveness in a representative sample of US hospitals. Using "best case" results can lead to an overestimation of a technology's benefit and cost-effectiveness. The entry criteria for efficacy studies of laparoscopy for ectopic pregnancy may produce a group of study patients who are not clinically similar to a true cross-section of patients with ectopic pregnancy in the United States. It would therefore not be appropriate to expect typical patients to be candidates for hospital discharge as soon as patients entered into laparoscopy studies.

Further study is needed to provide national estimates of successful ambulatory therapy for ectopic pregnancy, including estimates of patients receiving methotrexate treatment and those treated in free-standing surgery centers. While it is possible that ambulatory treatment has decreased hospital stays for ectopic pregnancy, there are no national data available to demonstrate this.

In 1990, 70% of patients admitted to a hospital for laparoscopic treatment of tubal pregnancy stayed longer than two days. Comparative hospitalization data from more recent years, when available, will help clarify whether there has been any reduction in hospital stays as practicing gynecologists have become more skilled in operative laparoscopy techniques.

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Conferences and Reviews

Fever, Rash, and Arthritis in a Woman With Silicone Gel Breast Implants

Discussant
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This discussion was selected from the diagnostic rounds at Stanford University Medical Center. It has been edited by Edward D. Harris, Jr., MD, Professor of Medicine.

(Genovese MC. Fever, rash, and arthritis in a woman with silicone gel breast implants. West J Med 1997 September; 167:149–158)

Case Presentation

The patient, a 44-year-old woman, was transferred to the Stanford University Medical Center, Palo Alto, California, for the evaluation of fever, rash, and arthritis. Her medical history began in 1990 when bilateral silicone gel breast implants were inserted for cosmetic reasons. These implants were replaced in January 1996, when capsular contracture and substantial hardening developed. About three weeks after the operation, the patient noted a rash under her left breast that spread rapidly to her torso and extremities. The rash was described as pink, maculopapular, nonconfluent, and mildly pruritic. She noted that it waxed and waned but usually was most prominent in the evenings.

In April 1996 she noted pain, stiffness, and swelling in the wrists, knees, ankles, and the interphalangeal joints of her hands. A persistent sore throat developed, and she had intermittent fevers to 38.9°C (102°F) that were more frequent and severe later in the day and often were accompanied by the rash. She treated herself with ice packs and topical emollients but achieved only minor relief.

In August 1996 the patient sought advice from her primary care physician when, in addition to the persistent rash and arthritis, her temperature rose to 40°C (104°F). She was admitted to an outside hospital for evaluation. Laboratory evaluation at that time was notable for a leukocytosis (leukocyte count, 23×10^9 per liter [23,000 per mm^3]), anemia (hematocrit, 0.30 [30%]), and elevated aminotransferase values (aspartate and alanine aminotransferase, both 120 units per liter). In addition, her serum alkaline phosphatase (400 units per liter) and γ-glutamyltransferase (GGT) levels were elevated. Biopsy of a left axillary lymph node showed only reactive hyperplasia. She had an extensive evaluation by a gastroenterologist in which an abdominal computed tomographic scan showed a 3-cm mass in the liver that was consistent with a hemangioma, and mild hepatic and splenic enlargement was noted. The results of colonoscopy, endoscopic retrograde cholangiopancreatography, and small bowel enteroclysis were all normal, and a viral hepatitis panel was negative. A liver biopsy specimen revealed a nonspecific inflammatory infiltrate.

All blood and stool cultures were negative for bacteria, fungi, fastidious organisms, ova, and parasites. A Venereal Disease Research Lab test, a rapid plasma reagin test, and serologic tests for Epstein-Barr virus, cytomegalovirus, Borrelia species, and parvovirus were all negative, and a lumbar puncture revealed no abnormalities.

Given the lack of any obvious infection, the patient's physicians searched for remote possibilities. She had emigrated from Korea (albeit 20 years previously with no recent foreign travel), and therefore scrub typhus was added to the list of possible diagnoses; the results of serologic tests for typhus returned negative as well. A gallium scan was done and showed increased uptake in the right frontal lobe of the brain, but findings were otherwise normal. Subsequent magnetic resonance imaging (MRI) of the brain revealed a parafalcine meningioma thought to be incidental. Despite the negative serologic studies, she was empirically treated with several antibiotic agents, including doxycycline, ofloxacin, vancomycin, clarithromycin, and ampicillin. Her fever did not resolve.

Immunologic tests revealed only an erythrocyte sedimentation rate (ESR) of 60 to 80 mm per hour and a low rheumatoid factor of 30 units by latex agglutination

*See also "Scleroderma and Silicone Breast Implants" by Donald Whorton, MD, MPH, and Otto Wong, ScD, on pages 159–165 and "Plaintiffs, Defendants, Lawyers, and Lawyers: Facts and Rumors About Silicone" by John S. Sergent, MD, on pages 182–183 of this issue of THE WESTERN JOURNAL OF MEDICINE.

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ABBREVIATIONS USED IN TEXT

ANA = antinuclear antibody
ASO = antistreptolysin O
DIC = disseminated intravascular coagulopathy
ESR = erythrocyte sedimentation rate
FDA = US Food and Drug Administration
GGT = γ-glutamyltransferase
MRI = magnetic resonance imaging
NSAID = nonsteroidal anti-inflammatory drug

(normal <40). An anti–smooth muscle antibody titer was positive at 1:80, but on repeat study was found to be negative. A comprehensive list of other negative assays is listed in Table 1. A hematologic workup for the patient's anemia included a bone marrow biopsy that showed both a normal marrow population and flow cytometric analysis of cells. The marrow had mildly decreased iron stores, and culture was negative for pathogens. She was empirically started on a short course of glucocorticoids; she subjectively improved and was discharged home.

In November 1996 the patient noted the return of the rash; temperatures from 39.4°C to 40.0°C (103°F to 104°F); bilateral arthritis involving her hands, wrists, elbows, and knees; and new symptoms of shortness of breath and cough. Again she received an exhaustive workup that was notable for new pleural effusions on physical examination and on the chest x-ray film. She was admitted to an outside hospital, and thoracentesis was done, which identified only a transudate that was culture-negative. An MRI of her thorax revealed an area of probable inflammation (3 cm in diameter) under the left breast implant. The ESR remained elevated in the range of 80 to 90 mm per hour, a ferritin level was 7,000 μg per liter (7,000 ng per ml), and an antistreptolysin O (ASO) titer was 170 units (normal ≤100). On hospital day 2, a regimen of methylprednisolone sodium succinate, 1 gram per day for three days, was started.

On the third hospital day, progressive mental status changes developed, categorized by the patient's physicians as severe encephalopathy, followed by hypoxemia and respiratory acidosis. An electroencephalogram showed global suppression without evidence of seizure phenomenon. An MRI of the head showed the parafalcine meningioma noted previously and no other abnormalities. Analysis of fluid from the lumbar puncture elicited the following values: protein, 2.78 grams per liter (278 mg per dl); glucose, 7.9 mmol per liter (142 mg per dl); leukocyte count, 22×10^6 per liter (22 cells per mm^3) (neutrophils, 0.62 [62%]; lymphocytes, 0.28 [28%]; monocytes, 0.10 [10%]); and erythrocyte count, 11×10^9 per liter (11,000 per mm^3). Gram's stain and culture were negative. Intravenous immune globulin therapy was then instituted at 400 mg per kg a day for 5 days. During this process the patient also had anasarca, worsening renal function (serum creatinine level, 186 μmol per liter [2.1 mg per dl]), proteinuria, low-grade disseminated intravascular coagulopathy (DIC), and pulmonary infiltrates on chest x-ray film. Plasmapheresis was initiated, and she was given fresh frozen plasma and cryoprecipitate. This resulted in an anaphylactic reaction that was treated with additional glucocorticoid therapy. The patient's mental state gradually improved, and she was continued on a regimen of methylprednisolone at 100 mg three times a day with abatement of the rash, fevers, and arthritis. Other studies included an elevated immunoglobulin E level (765 μg/l), a mildly abnormal C1q binding assay for immune complexes, and eosinophilia (4×10^6 per liter [400 per mm^3]). A second liver biopsy was unremarkable. The findings of a skin biopsy were consistent with leukocytoclastic vasculitis. The patient was then transferred to the Stanford University Medical Center for further evaluation.

TABLE 1.—*Negative and Normal Results of Autoimmune Workup*

Laboratory Study	*Finding*
Antinuclear antibody	Negative
Anti–double-stranded DNA antibody	Negative
Ribonuclear protein antibody	Negative
Anti–SSA (Ro)	Negative
Anti–SSB (La)	Negative
Anti–neutrophil cytoplasm antibodies	Negative
C3	Normal
C4	Normal
Total hemolytic complement (CH_{50})	Normal
C1q binding assay	Normal
Raji cell assay	Normal
Antimitochondrial antibody	Negative
Free thyroxine	Normal
Thyroid-stimulating hormone	Normal
Cryoglobulins	Negative

The patient was admitted to the medicine service at Stanford University. Physical examination and laboratory findings at presentation are listed in Tables 2, 3, and 4. At the time of the transfer, her chest x-ray film showed some improvement from previous films, but bilateral pleural effusions (left greater than right) persisted. There were no focal infiltrates. Initially her methylprednisolone treatment was continued at 100 mg given intravenously every 8 hours until all her data could be assimilated and the case reconstructed. Given her degree of anasarca, she was aggressively diuresed. A second bone marrow biopsy showed hypercellularity, numerous normal megakaryocytes, and decreased iron stores. She continued to have evidence of low-grade DIC with elevation in d-dimers and a low fibrinogen level; however, she never bled. An erythrocyte folate level, serum B_{12} level, haptoglobins, Coombs' test, and reticulocyte count were all normal. By hospital day 3, her steroid dosage was being tapered and her edema had lessened dramatically. The patient continued to improve

TABLE 2.—*Results of the Physical Examination*

Category	*Finding*
General	Patient appeared fatigued and edematous but not in distress
Vital signs	Temperature 36.8°C, blood pressure 140/78 mm of mercury, pulse 90 beats per minute, respiratory rate 16
Head	Normocephalic and atraumatic; pupils equal, round, reactive to light and accommodation; funduscopy revealed some narrowing of vessels; extraocular muscles intact and conjunctivae moist and noninjected; no evidence of patchy alopecia
Mouth	No evidence of thrush or lesion; mucous membranes were moist
Neck	Carotids had 2+ pulses without bruit; jugular venous distension to 8 cm above the sternal notch; thyroid gland was not palpable
Nodes	Bilateral axillary and anterior cervical chain lymphadenopathy 1 to 2 cm, tender
Breasts	Silicone breast implants bilaterally, with no erythema, warmth, or hardening
Lungs	Dullness to percussion in the bases bilaterally; decreased breath sounds in bases and crackles in the lower half of the lungs bilaterally to auscultation
Heart	Normal rate, regular rhythm, normal S1 and S2, no murmur, gallop, or rub audible
Abdomen	Liver edge palpable 2 cm below the right costal margin; stool Hemoccult-negative
Extremities	Anasarca with pitting edema in all four extremities
Neurologic	Nonfocal, with brisk reflexes, normal strength, normal gait and sensation
Joints	No evidence of synovitis with normal range of motion in all joints
Skin	No evidence of rash or excoriation

and was discharged to home ambulating and doing well, never having manifested fever, rash, or arthritis during her hospital stay. She was discharged on a slow prednisone taper from 60 mg per day. At her last visit to the clinic, 3 months after hospital discharge, she was taking 15 mg per day of prednisone and was asymptomatic.

Summary

Despite the long time course in this patient's presentation, a number of salient features were recurrent throughout her clinical course. Initially, and recurrently, a subtle rash developed primarily on the patient's torso. She had spiking fevers that were often more prominent in the evenings and seemed to herald the onset of the rash. Sore throat and arthritis also became commonplace for her. Her course waxed and waned over several months, and despite seeking medical care, she did not improve. The process was also accompanied by adenopathy and hepatosplenomegaly.

Although the patient's condition improved after a short course of glucocorticoids in the autumn, her illness then took on a more aggressive form. She had the development of pleural effusions, aseptic meningitis, anemia, leukocytosis, altered mental state, alterations in renal function, and edema. Not long after, she progressed to have hypofibrinogenemia, low-grade disseminated intravascular coagulopathy, and transient thrombocytopenia. This disorder precipitated several admissions to a hospital and culminated with aggressive intervention with high-dose glucocorticoids, intravenous immune globulin, and plasmapheresis.

TABLE 3.—*Chemical Laboratory Findings*

Test	*Value, SI Units* (Conventional Units)*
Electrolytes	
Sodium, mmol/liter	140 (140)
Potassium, mmol/liter	3.8 (3.8)
Chloride, mmol/liter	106 (106)
Carbon dioxide, mmol/liter	24 (24)
General chemistry	
Glucose, mmol/liter (mg/dl)	9.7 (174)
Urea nitrogen, mmol/liter (mg/dl)	16.8 (47)
Creatinine, µmol/liter (mg/dl)	115 (1.3)
Calcium, mmol/liter (mg/dl)	2.05 (8.2)
Phosphorus, mmol/liter (mg/dl)	0.97 (3.0)
Total protein, grams/liter (grams/dl)	54 (5.4)
Albumin, grams/liter (grams/dl)	30 (3.0)
Globulin, grams/liter (grams/dl)	24 (2.4)
Bilirubin, total, µmol/liter (mg/dl)	6.8 (0.4)
Aspartate aminotransferase, units/liter	52
Alanine aminotransferase, units/liter	53
Alkaline phosphatase, units/liter	63
Lactate dehydrogenase, units/liter	807
Creatine kinase, units/liter	35
Cholesterol, mmol/liter (mg/dl)	2.92 (113)
Special studies	
Rheumatoid factor, units/liter	<10
Ferritin, µg/liter (ng/ml)	985 (985)

*SI units are Système International units.

TABLE 4.—*Hematologic Laboratory Findings*

Test	*Value, SI Units* (Conventional Units)*
Hematocrit, factor of 1 (%)	0.21 (21)
Hemoglobin, grams/liter (grams/dl)	67 (6.7)
Platelets, $\times 10^9$/liter (10^3/mm^3)	123 (123)
Leukocytes, $\times 10^9$/liter (/mm^3)	5.9 (5,900)
Erythrocyte sedimentation rate, mm/hour	0
Differential cell count	
Neutrophils, factor of 1 (%)	0.82 (82)
Bands, factor of 1 (%)	0.01 (1)
Lymphocytes, factor of 1 (%)	0.09 (9)
Monocytes, factor of 1 (%)	0.08 (8)
Mean corpuscular volume, fl (μm^3)	80 (80)
Red cell distribution width, factor of 1 (%)	0.21 (21)
Coagulation	
Partial thromboplastin time, sec	32.8
Prothrombin time, sec	13.9
International normalized ratio	1.3
D-Dimer, μg/l	500 to 1,000
Fibrinogen, grams/liter (mg/dl)	0.98 (98)
Reptilase, sec	19.9*
Thrombin time, sec	18.3

*SI units are Système International units.

Discussion

MARK GENOVESE, MD: Could the disorder from which the patient suffers be silicone-related connective tissue disease? A widespread perception is that there is a direct relationship between silicone breast implants and connective tissue diseases. There are many reasons for this. Reports of cases of connective tissue diseases developing associated with silicone implants began to appear in the 1960s. This association first came into the public spotlight in December 1990, when CBS television news broadcast a segment titled "Hazards of Silicone Breast Implants." Since then silicone has drawn widespread attention in both lay and professional publications. Responding to growing concerns about the safety of silicone breast implants, the US Food and Drug Administration (FDA) in January 1992 announced a moratorium on the use of silicone gel breast implants until more information could be gathered about their safety. This moratorium was lifted in April 1992; at that time, however, the FDA acted to restrict the availability of silicone gel implants to controlled clinical trials.[1] In a class action lawsuit heard in the state of Alabama, the manufacturers of the silicone gel breast implants agreed to pay more than $4 billion to symptomatic implant recipients.

Given the perception of an association between silicone and connective tissue diseases, it is important to review the data to better facilitate an understanding of the problem. In the following section, several aspects of the problem will be addressed: the reported local reactions to silicone; the issues raised by the larger epidemiologic studies; and the symptoms, signs, and laboratory data frequently reported from symptomatic patients who have received silicone breast implants. These findings should be examined in the context of the case reported here. As well, no diagnosis can be arrived at without first working through a differential diagnosis, and I will do that, paying particular attention to the workup this patient received. Finally, I will discuss the probable diagnosis in this case and its implication for the treatment and prognosis of this patient.

Clearly local reactions to silicone do occur. Silicone is a polymer made through several chemical steps from the element silicon. The direct administration of silicone oils was popular in cosmetic surgery, particularly in the 1960s and 1970s. This practice continued for years, even after reports began to suggest that these oils led to local granulomatous reactions. In addition, these oils tended to migrate under the influence of gravity, leading to compression neuropathies and painful granulomas.[2] The most common local reaction to silicone breast implants is known as capsular contraction. This is a fibrotic reaction that occurs around the prosthetic envelope and leads to capsular shrinkage. It occurs to some degree in all patients with implants, leading to fibrotic changes palpable as firmness surrounding the breast implant.[3] In its severe form, there is extensive hardening of the surrounding breast tissue, severe tenderness, and a need for explantation. In addition to the local reaction to the silicone implant capsule, silicone oils may bleed through the cover of an intact silicone gel implant, causing local fibrotic and granulomatous changes.[3,4] If an implant ruptures, the silicone gel can produce local granulomata, fibrosis, and in some cases, a distant local reaction due to migration of the silicone.

A recently published (March 1997) population-based study looked at complications of silicone breast implantation that lead to additional surgery. Investigators reviewed the records of 749 women who lived in Olmsted County, Minnesota, and had undergone breast implantation at the Mayo Clinic between 1964 and 1991.[5] Of the 749 women, 208 (28%) underwent 450 additional implant-related operations. Of those, 91 were anticipated to be due to staged procedures or for changes related to size or cosmetic appearance. Of the 450 procedures, however, 359 were found to be related to complications from the previous breast implantation. The most common problem was related to substantial capsular contracture, affecting 131 of the 749 women (17.5%). Implant rupture and hematoma each resulted in 43 women requiring additional surgery. These data correlate with previous data and suggest that local complications related to silicone breast implants are common.[5]

In 1994, a review was published of all previously published case reports of associations between silicone and connective tissue diseases.[6] The authors reviewed both injectable substances and breast implants. A total of 293 patients were identified who had rheumatic symp-

toms after receiving silicone gel-filled implants. Of this group, 38 patients were given a diagnosis of scleroderma. Another 221 patients with gel-filled implants had symptoms that did not meet criteria for a diagnosable connective tissue disease. After reviewing animal studies, silicone immunogenicity, and the case reports, the authors came to the conclusion that silicone may elicit a local inflammatory response. The clinical, immunologic, and epidemiologic evidence, however, suggested no association between silicone and either a known or a novel connective tissue disease.[6]

The question plaguing practitioners and patients has not been whether silicone may cause a local inflammatory or granulomatous reaction, but whether silicone itself is a primary antigen or stimulus that leads to a systemic autoimmune or connective tissue disorder. What are the epidemiologic data? In 1994 a study was published that attempted to establish the risk of connective tissue diseases after breast implantation.[7] In this study in Olmsted County, Minnesota, 749 recipients of breast implants inserted between January 1964 and December 1991 were compared with 1,498 age-matched control women. Five cases of definite connective tissue disease were identified in the implant group, and ten cases were found in the control group. The conclusion was that there was no evidence of an association between silicone breast implants and connective tissue disease. In 1995 the results of the Nurses' Health Study cohort were published.[8] This study included 87,501 women, and of those, 1,183 had breast implants. With the use of questionnaires, it was determined that 516 women in this cohort of more than 87,000 had a definite connective tissue disease. Of these, only three in the group of 1,183 women with implants had a definite connective tissue disease, and all three had rheumatoid arthritis. No association was found between silicone breast implants and connective tissue diseases. In 1996 the FDA published a review of reported complications of silicone breast implants.[9] Cohort, case-study, and cross-sectional studies were reviewed. Study design, conclusions, and flaws were all summarized with the goal of addressing the reported relation between silicone and connective tissue diseases. The following conclusions were drawn[9(p 744)]:

> Information is insufficient to adequately advise women who currently have or are seeking to obtain breast implants about the overall risk of these devices. No epidemiologic study has indicated that the rate of well-defined connective tissue disease or breast cancer has greatly increased in women with silicone breast implants, but no studies have ruled out a moderately increased risk for these diseases. No studies have adequately addressed the crucial issue of local complications such as rupture and capsular contracture, although evidence increasingly points to a higher risk for rupture as implants age.

Available epidemiologic data suggest that there is no clear causal relationship between silicone breast implants and systemic connective tissue diseases. But is it possible that the patient in the case presented here does suffer from a silicone-related disorder? How well do her symptoms and signs correspond to those in published case series and anecdotal reports of silicone-related connective tissue disease?

The symptoms most often reported in symptomatic recipients of silicone breast implants include fatigue, arthralgia, and sicca-like symptoms. Data shown in Table 5 are representative. Similarly, the most common clinical signs reported in the same series (Table 6) included telangiectasias, erythema of the chest wall, and carpal tunnel syndrome.[10] From the data in Table 7, it can be seen that a spectrum of symptoms, signs, and laboratory data are reported between case series.[11] A careful review of the case report would suggest that the patient had few of the symptoms and signs outlined in Table 5 or Table 6 and few of the abnormal laboratory values listed in Table 8 during the course of her illness. This patient does not seem to fit the described profile of silicone-related connective tissue disease.

Part of the difficulty in establishing an association between silicone breast implants and connective tissue diseases has been that most of the symptomatic implant recipients fail to meet diagnostic criteria for known rheumatologic illnesses. Some authors have suggested that the constellation of symptoms and signs similar to those listed in Tables 5 and 6 could represent a new syndrome.[10–12] The vast spectrum of symptoms, signs, and laboratory tests that has been reported, however, and the differences among case series (Table 7) make it difficult to assign a single diagnostic syndrome. Although epidemiologic studies have not been designed specifically to address this issue, no study published to date has demonstrated any support for this theory. A recently published study looked for a relationship between breast implantation and connective tissue diseases.[13] In 1983,

TABLE 5.—*Symptoms in Patients With Silicone Breast Implants, n = 176*

Symptoms	*No. Patients (%)*
Chronic fatigue	135 (77)
Cognitive dysfunction	114 (65)
Arthralgia	98 (56)
Dry mouth	93 (53)
Dry eyes	88 (50)
Alopecia	71 (40)
Dysphagia	62 (35)
Photosensitivity	55 (31)
Myalgia	42 (24)
Raynaud's phenomenon	42 (24)
Serositis	30 (17)

Adapted from Solomon.[10]

TABLE 6.—*Physical Signs in Patients With Silicone Breast Implants, n = 176*

Signs	*No. Patients (%)*
Telangiectasias	105 (60)
Erythema of chest wall	99 (56)
Carpal tunnel syndrome	83 (47)
Petechiae	81 (46)
Enlarged lacrimal glands	45 (26)
Tender thyroid	38 (22)
Enlarged thyroid	37 (21)
Enlarged parotid	31 (18)

Adapted from Solomon.[10]

an inception cohort was established to observe the outcome of patients with early signs and symptoms of undifferentiated connective tissue diseases. A total of 410 subjects were enrolled between 1983 and 1987. Of the 410 patients, 197 satisfied criteria for specific connective tissue diseases: rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, or polymyositis or dermatomyositis. The remaining 213 patients were classified as having undifferentiated disease. Of the 410 patients, 323 were women. Of this group, only three had undergone breast implantation, one of whom had symptoms before implantation. All three women were classified in the undifferentiated group. The data failed to confirm any relationship between early symptoms of differentiated or undifferentiated connective tissue diseases and breast implants.[13]

If the patient in the case presented here does not have a connective tissue disease related to her silicone breast implants, what is her illness? First is the possibility of an infectious cause. After the initial evaluation, including Gram's stains and cultures, was negative, the likelihood of a bacterial infection—that is, perioperative wound infection, endocarditis, sepsis—seemed less likely. Attention then turned to more fastidious organisms such as mycobacteria. This patient showed no evidence of tuberculosis by skin tests (purified protein derivative), sputum tests, or bone marrow examination. Viral, parasitic, and spirochetal causes were considered. She had negative serologic tests for parvovirus B19, cytomegalovirus, and Epstein-Barr virus; tests for ova and parasites, malaria, rapid plasma reagin, and Lyme titer were all negative. Given her Asian ethnicity, scrub typhus was also considered and ruled out.

A lymphoproliferative process was also considered. Although lymphadenopathy and persistent abnormalities were found in the blood count (leukocytosis, thrombocytosis, and anemia), lymph node and bone marrow biopsies failed to confirm those suspicions. Given the presence of obvious organomegaly and abnormal results on liver function tests, the differential diagnosis included viral and autoimmune hepatitis, sclerosing cholangitis, and primary biliary cirrhosis. Numerous imaging studies, biopsies, and endoscopic retrograde cholangiopancreatography failed to shed light on the underlying cause of this patient's persistent illness.

Attention was then focused on diffuse connective tissue diseases. First thoughts usually include systemic lupus erythematosus, rheumatoid arthritis, and vasculi-

TABLE 7.—*Clinical Findings From Several Series of Silicone Implant Recipients*

Findings	*Vasey*	*Salaman*	*Freundlich*	*Barenstein*	*Total*
Patients, no.	50	176	50	100	376
Fatigue, %	84	77	88	91	83
Arthralgias, %	60	56	74	69	62
Myalgias, %	84	24	74	62	49
Cognitive dysfunction, %	—	65	—	13	46
Xerostomia or sore throat, %	—	53	50	26	44
Alopecia, %	—	40	38	35	38
Skin rash, %	10	46	36	15	36
Adenopathy, %	38	—	44	30	35
Arthritis, %	42	—	42	21	31
Fever, %	10	—	26	31	23
Raynaud's phenomenon, %	14	24	24	8	20
Antinuclear antibody, no. positive/no. tested (%)	11/41(26)	44/176 (25)	10/50 (20)	22/84 (26)	25
Elevated ESR, no. positive/no. tested (%)	7/40 (36)	57/176 (32)	4/50 (8)	14/76 (18)	24
Rheumatoid factor, no. positive/no. tested (%)	5/33 (15)	5/176 (3)	10/50 (20)	9/71 (12)	9

ESR = erythrocyte sedimentation rate
Adapted from Borenstein.[11]

TABLE 8.—*Laboratory Findings in Patients With Silicone Breast Implants*

Laboratory Findings	*Patients, %*
Erythrocyte sedimentation rate >25 mm/h	32
Immunoglobulin (Ig) M elevated >2.8 grams/liter (>280 mg/dl)	28
Antinuclear antibody ≥1:40	25
IgA elevated >4.5 grams/liter (>450 mg/dl)	8
Antimicrosomal antibody	6
IgG elevated >18 grams/liter (>1,800 mg/dl)	4
Rheumatoid factor >40	3
Anti-SSB (La)	2
Anti-SSA (Ro)	1

Adapted from Solomon.[10]

TABLE 9.—*Joint Involvement in Patients With Adult-Onset Still's Disease, n = 62*

Joint Involved	*No. Patients (%)*
Knee	51 (82)
Wrist	45 (73)
Ankle	34 (55)
Proximal interphalangeal	29 (47)
Elbow	27 (44)
Shoulder	25 (40)
Metacarpophalangeal	22 (35)
Metatarsophalangeal	11 (18)
Hip	7 (11)
Distal interphalangeal	6 (10)
Interphalangeal	2 (3)
Temporomandibular	2 (3)

Adapted from Pouchot et al.[19]

tis. None of these fit the clinical picture. The patient was negative for antinuclear antibody (ANA) and failed to meet the clinical or research criteria for systemic lupus erythematosus.[14] Rheumatoid arthritis and vasculitis did not adequately explain her manifestations or clinical course. More remote possibilities were considered, including parvovirus B19, cryoglobulinemia, and serum sickness, but the clinical presentation and laboratory test results did not fit any of these either. Rheumatic fever was a possibility, but the patient failed to meet Jones criteria for the diagnosis of rheumatic fever.[15]

One connective tissue disease, however, appears to be a probable diagnosis in this woman: adult-onset Still's disease. This disorder is a systemic inflammatory illness accompanied by the hallmark signs of spiking fever, rash, and polyarthritis.[16] The symptoms and signs are identical to those seen in children with systemic juvenile-onset rheumatoid arthritis or Still's disease. The mean age of onset of the adult version is 29.9 years plus or minus 12.4 years, and it affects both sexes equally.[17] The mean delay in arriving at the diagnosis may be as long as 16 months.[18] The clinical features commonly include high spiking fever (often accompanied by a sore throat); arthritis; and a subtle, fleeting, erythematous salmon-colored rash typically referred to as "evanescent." On occasion, patients may present with only a rash and fever. Both often become more prominent in the evenings. The rash typically involves the torso and extremities.[16] Although classically described only as maculopapular, the rash may be pruritic 30 to 40% of the time.[18,19]

Musculoskeletal manifestations are present at some point in virtually every patient with adult-onset Still's disease. In addition to arthralgia and myalgia, oligoarticular or polyarticular arthritis is almost always found. It commonly affects the knees, wrists, ankles, and proximal interphalangeal joints and less commonly the hips and shoulders (Table 9).[16,20] The accompanying synovitis is usually mild and transient, although a few patients have had measurable radiographic progression of arthritis. Of these, most had a good functional prognosis.[16,18] Carpal ankylosis may occur occasionally and has been described as a diagnostic sign in adult Still's disease.[16,20–22] Other patients may have ankylosis of the cervical spine. Synovial fluid analysis often reveals a high leukocyte count with a predominance of neutrophils.[19,20,22]

Other common symptoms and signs appear with adult-onset Still's disease (Table 10). A persistent or waxing and waning sore throat is common; lymphadenopathy and hepatosplenomegaly are among these, as is serositis (such as pleuritis and pericarditis).[17,19,20,23] Less common manifestations are listed in Table 11.

Do data from the laboratory evaluation help to confirm a diagnosis of Still's disease in adults (Table 12)? Patients frequently will show increases in the ESR, leukocytosis with a predominance of neutrophils, and normocytic, normochromic anemia.[16] Hepatocellular dysfunction is common; aminotransferase levels are frequently elevated, and patients occasionally have elevated alkaline phosphatase and GGT levels.[18,20,21] Four-fifths of patients will have difficulty with synthetic liver function leading to low serum albumin levels and coagulopathy with elevation in the international normalized ratio (INR).[20] Still other patients will become hypofibrinogenemic, and mild DIC and occasionally transient thrombocytopenia will develop.[17,19,22,24] The ASO titers may be mildly elevated, but ANA and rheumatoid factor are normal or only slightly abnormal. More recently, serum ferritin values have been found to be markedly elevated in patients with Still's disease, with values sometimes exceeding 20,000 μg/l.[17,25] Often the levels will exceed 10 times the normal value and have been shown to correlate with disease activity.[17,26]

How is the diagnosis of adult-onset Still's disease made? It is a clinical diagnosis based on a constellation of symptoms and signs and usually is made by exclu-

TABLE 10.—*Clinical Manifestations of Adult-Onset Still's Disease, n = 288*

Manifestations	*Patients, %*
Arthralgia	99.6
Fever ≥39°C (≥102°F)	95.7
Arthritis	94.3
Typical rash	88.5
Lymphadenopathy	60.3
Sore throat	57.9
Splenomegaly	51.7
Hepatomegaly	40.6
Weight loss ≥10%	38.3
Deforming arthritis	31.0
Pericarditis	27.8
Pleuritis	24.6
Abdominal pain	13.2
Pneumonitis	12.8
Renal involvement	10.7

Adapted from Ohta et al.[17]

sion. Paramount is the exclusion of other infectious, inflammatory, and neoplastic diseases as previously outlined. Patients often will present in their third or fourth decade of life with persistent fever, rash, and arthralgia or arthritis.[16] A patient will often have a sore throat and evidence of lymphadenopathy and hepatosplenomegaly. The most specific finding is the evanescent skin rash that is more obvious later in the day.[27] The laboratory abnormalities are nonspecific.

Unfortunately, the cause of Still's disease remains unknown. Although infectious causes, particularly viral (such as rubella or echovirus), have frequently been proposed, studies to date have failed to elicit any conclusive correlations. Investigators have also focused on a possible non-necrotizing, immune complex–mediated vasculitis; however, complement assays and skin biopsies have not adequately supported this theory.[21] Genetic predispositions have also been postulated. Investigators have examined HLA genotypes, but no consistent correlations have been established.[19,21]

Initial criteria for the diagnosis of adult-onset Still's disease were proposed by Bywaters in 1971 in a classic article discussing Still's disease in adults; they included high temperatures, transient rash, and arthritis.[16] Several authors since then have created their own variations on these criteria.[22,23,28,29] An effective set of criteria for diagnosis is listed in Table 13.[27] These were established by assessing the most common clinical features in 90 cases of Still's disease and comparing them with the clinical features of 267 control patients with other autoimmune or connective tissue diseases. In this series, all criteria were discussed, and the sensitivity, specificity, relative value, likelihood ratios, and accuracy for each were established. The performance of these criteria is included in Table 14.[27]

TABLE 11.—*Rare But Reported Manifestations of Adult-Onset Still's Disease*

Central nervous system
Peripheral neuropathy
Adult respiratory distress syndrome
Congestive heart failure
Disseminated intravascular coagulopathy
Thrombocytopenia
Subcutaneous nodules
Necrotizing lymphadenopathy

How does the patient's illness in this case presentation fit into the criteria described above? First and foremost, after a thorough evaluation, the patient was without evidence of infection, cancer, or rheumatic disease. Her clinical course suggests that she meets all of the major and minor criteria listed in Table 13. While this does not prove that the patient is suffering from adult-onset Still's disease, it suggests that it is the most appropriate diagnosis, given her clinical presentation and course. Although it may appear that it took too long to reach this conclusion, it is important to realize that the mean delay in reaching the diagnosis recorded in the literature is as long as 16 months.[18] In retrospect, our patient appears to have manifested the classic symptoms, signs, and laboratory features of adult-onset Still's disease. Even if it had been clear from the beginning that she might be suffering from Still's disease, the diagnosis could not have been made until all the other possible causes had been adequately excluded. The difficulty in arriving at this diagnosis highlights the fact that adult-onset Still's disease is poorly understood, and even among physicians and the medical community, it is not well recognized. While her hospital course was severe and troubling, other similar cases have been reported in the literature.[24] Fortunately, this patient responded to the aggressive interventions undertaken by her physicians,

TABLE 12.—*Laboratory Findings in Patients With Adult-Onset Still's Disease, n = 288*

Laboratory Findings	*Patients, %*
ESR ≥40 mm/hour	96.7
Negative antinuclear antibody	93.2
Negative rheumatoid factor	92.4
Leukocytes ≥10 × 10^9/liter (≥10,000/mm^3)	91.7
Albumin ≤35 grams/liter (≤3.5 grams/dl)	80.0
Elevated hepatic enzymes	71.6
Hemoglobin <100 grams/liter (<10 grams/dl)	68.0
Leukocytes ≥18 × 10^9/liter (≥18,000/mm^3)	60.0
Neutrophils ≥0.90 (≥90%)	35.0

ESR = erythrocyte sedimentation rate
Adapted from Ohta et al.[17]

TABLE 13.—*Criteria* for the Classification of Adult-Onset Still's Disease*

Criterio	*Description*
Major	Fever to 39°C (102°F) >1 week
	Arthralgia >2 week
	Typical rash
	Leukocytosis (>10 × 10^9/l with >0.80 neutrophils)
Minor	Sore throat
	Lymphadenopathy with or without splenomegaly
	Liver dysfunction
	Negative rheumatoid factor and antinuclear antibody tests
Exclusions	Infections
	Malignant neoplasms
	Rheumatic diseases

*Five or more criteria, including two or more major criteria, are required for the classification of adult-onset Still's disease.
Adapted from Yamaguchi et al.[27]

TABLE 14.—*Performance of Criteria for Adult-Onset Still's Disease**

Application of Eight Criteria	*Sensitivity, %*	*Specificity, %*
When criteria given equal weight		
≥4 Criteria	100.0	75.0
≥5 Criteria	96.2	89.6
≥6 Criteria	83.0	98.2
When divided into four major and four minor criteria		
≥2 Major and ≥2 minor	98.1	85.4
Total ≥4 with ≥2 major	100	84.1
Total ≥5 with ≥2 major	96.2	92.1

Adapted from Yamaguchi et al.[27]
*The data reflect the application of criteria to 53 patients with definite Still's disease and 164 control patients.

and at the time this report was compiled, 12 weeks after discharge, she appears to be doing well. She has responded well to a slow and gradual reduction in the dosage of her oral glucocorticoid and has not required the use of a second-line agent.

What is the appropriate treatment of this disorder once the diagnosis is made? Because there is no known cause, treatment is empirical. Still's disease is frequently a self-limited illness that follows a remitting course. Thus, the treatment course in many patients need not be a long one. Patients will often follow a polycyclic pattern with remissions and exacerbations.[21] Nonsteroidal anti-inflammatory drugs (NSAIDs) have classically been described as the first-line treatment option; yet, the literature suggests that high-dose salicylates or NSAIDs are effective in only 20% of patients.[19,22] Patients for whom NSAID therapy fails and those with severe disease will need glucocorticoid therapy. Prednisone should be given in a dose of 1 to 2 mg per kg a day, although some patients may do well with smaller doses. For those patients with severe disease and those who cannot be successfully tapered off glucocorticoids, alternative agents need to be considered. In those with persistent mild disease, despite adequate trials of glucocorticoids, or those who have a flare while the drug doses are being tapered, hydroxychloroquine sulfate has been advocated as a useful adjunct. In addition, intramuscular gold salts, sulfasalazine (salazopyridine), and penicillamine have all been used in patients with persistent disease. The most-often-used second-line agent has been intramuscular gold; this has been associated with a 40% improvement rate.[19] More recently, methotrexate has been useful for articular and systemic manifestations of adult-onset Still's disease and has been a useful "steroid-sparing" agent.[18,26] Azathioprine and cyclophosphamide have been used, but their use should only be considered in cases of severe or refractory disease.[30,31]

How about prognosis? Most patients do well with only limited functional disability from their disease.[16,23] A small fraction will go on to have serious arthritis and ankylosis. This subset can often be identified relatively early as those with polyarticular onset, hip involvement, and disease requiring glucocorticoid therapy for longer than two years.[23] A retrospective series designed to assess the long-term prognosis in patients with Still's disease compared patients with a mean duration of disease of 10 years with same-sex sibling controls. Of patients 5 or more years from the initial diagnosis, 50% were no longer taking medication. Patients with Still's disease were found to have higher levels of pain, physical disability, and psychological disability than controls; however, the levels of pain and disability were low when compared with those of other rheumatic diseases.[32]

The patient discussed in this review suffered from a progressive, indolent disorder that provided a substantial diagnostic dilemma for those involved in her care. She underwent an extensive diagnostic evaluation, and only through a process of exclusion was the appropriate diagnosis reached. Although she did undergo bilateral silicone gel breast implantation before the onset of the disorder, there is little anecdotal or epidemiologic evidence to support that she had a systemic connective tissue disease related to the breast implantation. What this patient did suffer from was a systemic inflammatory illness accompanied by spiking fevers, rash, and polyarthritis. Based on the constellation of symptoms, signs, and laboratory data, it appears that she had adult-onset Still's disease. Her lack of polyarticular onset, no hip involvement, and a good response to steroid therapy with a relatively quick taper of the dosage all suggest that she will have a good functional outcome.

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Scleroderma and Silicone Breast Implants

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Scleroderma, a systemic connective tissue disease, is relatively rare. Case reports of women with silicone breast implants who have developed scleroderma began appearing in the US medical literature in the 1980s. By mid-1993, of the 72 case reports of women with breast implants and connective tissue disease, 38 were reported to have scleroderma. As a result of the publication of these case reports, a number of epidemiologic studies were conducted to find out if silicone breast implants are associated with the development of scleroderma. Five case-control studies of scleroderma were done, plus four prospective studies of connective tissue diseases (including scleroderma) and breast implants. In eight other epidemiologic studies, no cases of scleroderma were identified among women with breast implants. This article includes a qualitative review of the epidemiologic studies and a quantitative summary (meta-analysis) of the case-control studies. Neither the case-control studies nor the other epidemiologic data support the hypothesis that scleroderma is associated with or causally related to breast implants.

(Whorton D, Wong O. Scleroderma and silicone breast implants. West J Med 1997 September; 167:159–165)

Silicone, which has been considered to be biologically inert, has been used in many different types of medical devices, including tubing, breast implants, joint implants, penile implants, artificial heart valves, intraocular lenses, ventriculo-peritoneal shunts, artificial testes, needles, and baby bottle nipples. Silicone breast implants (SBIs) were introduced into the commercial marketplace in 1962; since that time, they have been used for postmastectomy reconstruction and cosmetic breast enhancement.

The most common type of breast implant consists of a gel of polydimethoxysiloxane (PDMS) enclosed in an envelope made of a more highly cross-linked PDMS combined with amorphous (fumed) silica to provide strength. Some breast implants contain saline instead of PDMS, and others use polyurethane for the envelope. Paraffin, silicone, and other materials have also been used for breast enhancement.

Estimates are wide-ranging of how many women in the US have received SBIs or similar implants since 1962. Bright et al., in a 1993 report from the National Centers for Health Statistics,[1] cited an estimate of 304,000 women through 1988; a 1992 report from the Food and Drug Administration[2] estimated 1–2 million women in the United States and Canada; Terry et al.[3] estimated the number of women with breast implants to be approximately 900,000. A difficulty in reaching an accurate estimate is that both manufacturers and plastic surgeons count the number of implant units. Some women have repeated implant surgeries, and others have only unilateral implants, so the number of implant units is not the same as the number of women with implants. The figure of 1–2 million women with implants in the US and Canada appears to be the most frequently cited. Within the US, a higher percentage of women in the West and South have implants than in the East and Midwest. In any event, it can be stated that a large number of women in the US have undergone breast implants. Therefore, any potential health problems associated with breast implants can affect a large number of women, particularly in the West and South.

Scleroderma (systemic sclerosis) is a connective tissue disease (CTD) with skin manifestations and systemic effects. In 1980, the American College of Rheumatology (ACR)[4] developed the following criteria for scleroderma diagnosis: the presence of proximal skin scleroderma or two of the following three symptoms: sclerodactyly, digital pitting scars/pulp loss, and bibasilar pulmonary fibrosis. A milder version of scleroderma called CREST is based on five symptoms: calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia.

Another condition also called scleroderma is limited to the skin, especially of the digits and hands, without

*See also "Fever, Rash, and Arthritis in a Woman With Silicone Gel Breast Implants" by Mark C. Genovese, MD, on pages 149–158 and "Plaintiffs, Defendants, Lawyers, and Lawyers: Facts and Rumors About Silicone" by John S. Sergent, MD, on pages 182–183 of this issue of THE WESTERN JOURNAL OF MEDICINE.

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Note: Dr Whorton has consulted to attorneys for Dow Corning Corporation and, in California, to attorneys for six different plastic surgeons being sued for malpractice. Prior to May 1995, he testified at one trial and was deposed on three cases related to silicone breast implants. Dr Wong has consulted to attorneys representing Bristol Myers Squibb since 1995. He testified at one trial and was deposed on one case.

internal involvement. This localized condition is also called morphea. Generally, and in this article, scleroderma is used for the systemic condition, either systemic sclerosis (SSc) and/or CREST, and does not include the condition limited to the skin.

Scleroderma is relatively rare, which is another difficulty with determining accurate incidence rates. Most of the data are projected from university hospitals or similar clinical settings, where large numbers of scleroderma patients are diagnosed and treated.[5] The estimated incidence rate ranges from 2 to 10 cases per million; although data from the University of Pittsburgh suggest a higher incidence rate of 20 per million. Women develop the disease about three times more frequently than men. At younger ages (under 40), the difference between females and males is 7:1. African-Americans have a higher rate of the disease than whites. The disease occurs more frequently in women in their fifth and sixth decade of life.

Scleroderma appears to be a condition in which initial symptoms predate the diagnosis of the disease by a considerable period of time—an average of 6 years.[6]

Many environmental agents are reported to be associated with the development of scleroderma, although many of these relationships have been based on primarily case reports and have not been systematically studied. The agents include polyvinyl chloride, crystalline silica (especially in cases of pulmonary silicosis), rapeseed oil (with aniline), and drugs such as hydralazine and procainamide. Many of the reports on these environmental agents predated the ACR definition of scleroderma, so diagnosis in these reports might not have been consistent or uniform. Many of the conditions have also been primarily limited to the dermal manifestations. Finally, with drugs and some environmental agents, the dermal effects can dissipate after cessation of exposure.[5]

There have been a number of case reports on women with silicone breast implants and connective tissue disease in general and with scleroderma in particular. The first case report of CTD occurring in a woman with previous breast enhancement injections was published in 1964. By 1984, the number of CTD cases in women with breast implants reported in the published literature had reached 46, eight of which had been diagnosed with scleroderma. Of those eight, one had known injection with silicone, four with paraffin, and three with unknown materials.[7]

The first case report of CTD and silicone breast implants to appear in the US medical literature was reported in 1982 by Van Nuven et al.[8] The authors reported one case of systemic lupus erythematosus (SLE), one with mixed connective tissue disease, and one with a combination of rheumatoid arthritis and Sjogren's syndrome, but no scleroderma. In 1988, Spiera[9] reported five scleroderma patients who had breast implants. More recently, Sanchez-Guerrero et al.[10] summarized case reports in the literature as of mid-1993. Of the 72 definite and possible cases of reported CTDs in women with breast implants, 38 were diagnosed with scleroderma.

Subsequent to the publication of those case reports, a number of epidemiologic studies were conducted here and abroad. In this article, we review and summarize all pertinent epidemiologic studies on the issue of breast implants and scleroderma. Although a review and meta-analysis on the relationship between breast implants and three major connective-tissue diseases (scleroderma, systemic lupus erythematosus, and rheumatoid arthritis) was conducted by Wong[11] in 1996, the present report includes some final data from one study and more complete data from a second study that were not available to Wong at the time of his review. Thus, for scleroderma, the present report provides an update to the previous review.

Review of Case-Control Studies

Because of the rarity of scleroderma, the case-control (case-referent or retrospective) study design is the most appropriate epidemiologic approach for studying the relationship between breast implants and scleroderma. Case-control studies are more powerful (statistically speaking) and more efficient for studying rare diseases than cohort (prospective) studies. Five case-control studies have been completed and published. In addition, there are prospective studies and other investigations that can be used to augment the case-control studies.

Burns et al.

Burns et al.[12] used a population-based case-control study design to investigate scleroderma cases and breast implants in Michigan women diagnosed during 1980–1991. Cases were identified through major hospitals, scleroderma referral centers, practicing rheumatologists, and the United Scleroderma Foundation of Southeast Michigan. The 377 cases were estimated to represent 83% of all scleroderma patients in the state during that period. Scleroderma cases included those who had both classic ACR and the CREST variant. Limited dermal scleroderma cases were not included. Diagnostic information was verified by reviewing medical records. The 1184 controls were recruited through use of the random digit telephone dialing technique in sampling. Each eligible control completed a questionnaire administered over the telephone.

The analysis was limited to 274 cases from 1985 to 1991 because of questionable completeness of the earlier data. Two cases and 14 controls had undergone breast implantation. Of the 14 controls, 12 had silicone gel breast implants. The two scleroderma cases with silicone gel breast implants were diagnosed 1 and 12 years after the procedure. The odds ratio (OR) adjusted for age, race, and income between breast implants and scleroderma and the corresponding 95% confidence interval (95% CI) were 0.95 and 0.21–4.36. When the analysis was restricted to silicone gel breast implants only, the unadjusted OR was 0.72 (0.16–3.32) and the adjusted OR, 1.30 (0.27–6.23).

Burns et al. also reported that exposures to chlorinated solvents and certain jobs and hobbies that might involve exposure to solvents were found to be positively associated with scleroderma. In addition, they found that the use of antacids was significantly higher among the scleroderma patients (adjusted OR 1.83 [1.19–2.82]). When the data included only respondents who reported using antacids more than 2 years before diagnosis, the resulting OR of 1.40 was no longer statistically significant. These findings imply that in scleroderma, a slowly developing disease, the use of antacids may be an indicator of esophageal involvement in the disease process, as opposed to antacids being the etiologic factor of scleroderma.

Englert and Brooks

Englert and Brooks[13] studied scleroderma and breast implants among women in Sydney, Australia, in a case-control study. Women diagnosed with scleroderma during 1974–1988 were identified through a variety of sources: death certificates, hospitals, private practices, medical laboratories performing antinuclear antibody (ANA) tests, and the Scleroderma Association. Age-stratified controls were obtained from patients of 28 randomly chosen private medical practitioners in Sydney.

Information on breast implant status was obtained through a telephone questionnaire specifically designed for the study. This study, reported in 1994, included only cases from women who were alive at the time of the interview (the study was subsequently continued, as described below). There were 251 cases and 289 controls. Scleroderma cases included those with classic ACR criteria as well as CREST.

The unadjusted rates for augmentation mammoplasty were 1.59% among the scleroderma cases and 1.73% among the controls, OR 0.89 (0.23-3.41). Two of the four scleroderma cases with augmented mammoplasties had symptoms before the augmentation procedure, and two had no evidence of the disease at the time of the surgery for breast implants. The authors also found an increase in antacid use but did not truncate their analysis as was done by Burns et al.

Englert, Morris and March

The Englert, Morris and March[14] investigation was a continuation of the study described above. The purpose was to objectively validate all self-reported information on implant status, date of implant, and onset of disease, and to obtain data from the deceased or previously untraceable cases. For deceased cases, the authors were able to review medical records. For live cases, they were prohibited from reviewing medical records and relied on the review of the women's private practitioners. Medical records were reviewed for 21 of the 27 women who were untraceable. Implant information was obtained from the surgeons who performed the procedure.

Cases and controls were re-interviewed by researchers who were blinded to the response of the data validation from the general practitioners or surgeons. The researchers also validated the onset of symptoms and the date of the scleroderma diagnosis from medical records. The first symptom was usually Raynaud's phenomenon, and the second symptom was from either the skin or the upper gastrointestinal system.

The authors were able to validate the following: 287 of the 305 living cases, all 224 deceased cases, and 21 of the 27 untraceable cases. The 18 living nonparticipants were similar in age to the 287 living participants. For self-reported augmented mammoplasty status (presence or absence), they validated 532 of the 556 cases (95.7%) and 252 of the 289 controls (87.9%). There were five scleroderma cases and four controls with augmented mammoplasties. One additional control patient and her general practitioner denied that she had ever had an augmented mammoplasty. Only three of the five scleroderma cases had the mammoplasties before the onset of symptoms.

Analysis of the data included those cases who developed symptoms after the augmentation mammoplasty compared to the four controls, which showed an unadjusted OR of 0.66 (0.16–3.86) and an adjusted OR of 0.52 (0.11–2.41). The timing of the onset of first symptoms for these three cases were 4 months, 8 years, and 10 years; for date of scleroderma diagnosis after surgery, 5 years, 10 years, and 3–5 years.

Hochberg et al.

Three geographic areas were included in the multicenter case-control study of scleroderma and breast implants reported by Hochberg et al.[15]: Scleroderma Center patients referred by rheumatologists from the Baltimore-Washington metropolitan area and patients who were members of the greater Washington, DC, chapter of the Scleroderma Foundation; patients seen by members at the Division of Rheumatology and Clinical Immunology at the University of Pittsburgh, Pennsylvania, area; and patients seen by members of the Division of Rheumatology, University of California, San Diego, or by community rheumatologists in San Diego and Orange Counties, California. Each of the cases had the clinical diagnosis of scleroderma, and each was mailed a questionnaire during 1990 and 1991. Completion rates varied by geographical region: 61.9% in Baltimore-Washington, DC, 78.4% in Pittsburgh, and 100% in San Diego-Orange County. From the three areas combined, 837 women were diagnosed with scleroderma in 1991 or earlier.

Age-stratified controls were recruited from each geographic location through the use of the random digit telephone dialing technique. Each of the 2507 eligible controls completed a telephone-administered questionnaire. The median number of controls per case was three (range 0–4). Hochberg et al. performed two analyses: an unmatched analysis using multiple regression of all cases and controls with adjustments for age, race, and geographic location and a matched analysis using conditional logistic regression, excluding cases without matched controls. Eleven scleroderma patients had

breast implants before the diagnosis of scleroderma (1.31%). Thirty-one of the controls had breast implants (1.24%). The unmatched OR was 1.07 (0.53–2.13), and the matched OR, 1.11 (0.55–2.24). A subsequent set of analyses was performed after excluding 35 cases whose scleroderma diagnosis was made before 1962 (when silicone breast implants were introduced). The unmatched OR was 1.08 (0.53–2.17), and the matched OR, 1.10 (0.54–2.23).

Goldman et al.

Goldman et al.[16] studied all the patients of one rheumatology practice in Atlanta, Georgia, who were seen between 1986 and 1992 and whose records had been computerized since 1985. The database contained 4229 female rheumatology patients. Independent chart reviews were conducted to confirm the rheumatologic diagnoses in the database.

Of the 4229 female patients, 721 were diagnosed with rheumatoid arthritis and/or one of the connective tissue diseases, including 64 who were diagnosed with scleroderma. One hundred and fifty were identified to have undergone breast implants, including 12 who were diagnosed with rheumatoid arthritis and one with connective tissue disease. A series of analyses were performed to evaluate the risk of silicone breast implants and various categories of CTD. Patients in the database without a diagnosis of rheumatoid arthritis or one of the connective tissue diseases were used as controls. None of the 64 scleroderma patients had undergone breast implants; the adjusted OR was 0.00 (0.00–2.04).

Review of Prospective Studies

In addition to case-control studies, a number of prospective studies of women with breast implants have been conducted. Prospective studies have the advantage of being able to examine a wide range of CTDs. For specific entities such as scleroderma, however, which are relatively rare, the statistical power of these prospective studies in detecting a modest increase in risk due to breast implants is usually low. Some prospective studies relied on self-reported diagnoses of CTD, thus suffering from the lack of diagnostic confirmation.

Gabriel et al.

Gabriel et al.[17] conducted a population-based prospective study of women with breast implants in Omstead County, Minnesota, from 1962 through 1991. The authors used the medical record database from the Mayo Clinic and its affiliated organizations to identify 749 women with breast implants. From the same database, 1498 matched controls were selected. The cases had been followed for an average of 7.8 years since the time of implant. Examination of medical records showed that five of the 749 implanted women had a connective tissue disease, and 10 of the 1498 controls had a connective tissue disease. None of the implanted women had scleroderma; systemic sclerosis with polyarthritis was present in one of the controls.

Hennekens et al.

This prospective study (known as the Women's Health Cohort Study)[18] was designed to be a randomized, double-blinded, placebo-controlled trial originally to evaluate the benefits and risks from low-dose aspirin, beta-carotene, and vitamin E in the primary prevention of cardiovascular disease and cancer among ~40,000 female health professionals ages 45 and older. From September 1992 to May 1995, the authors mailed questionnaires to 1.75 million female health professionals. Included in the questionnaire were questions about breast implants and various CTDs, including scleroderma. By August 1995, questionnaires were returned from 426,774 (24.4%) women ages 18 to 99 years. After eliminating those with incomplete information or who had either implants or CTD diagnosed before 1962, the researchers were left with 395,528 (22.6%) women in the cohort.

The questionnaire contained inquires about 38 different diseases and surgical procedures, including various categories of CTD. The breast implant questions contained inquires about dates of the procedures but no questions about type of implants, reason for the procedure, unilateral or bilateral, ruptures, etc. There was no validation for any of the questionnaires' responses. Follow-up began in 1962 or whenever the woman reached age 18. A sizable portion (30% overall) of the population did not include any dates of diagnosis on the questionnaire. Those individuals were not included in the analyses.

There were 10,830 reported breast implants among the 395,528 women (2.74%). Within the cohort, 324 women self-reported having scleroderma. Among the women with reported scleroderma, 10 had breast implants and 314 did not. The relative risk (RR) for having scleroderma and breast implants was 1.84 (95% CI 0.96–3.48). In an analysis for years since implant, the authors reported the following RRs: 2.66 (1.11–6.51) for 0–4 years, 0.60 (0.83–1.56) for 5–9 years, and 2.06 (0.77–5.61) for >10 years. Analysis by age reported RRs for breast implants and scleroderma of 1.94 (0.91–4.15) for ages younger than 50 and 1.63 (0.52–5.17) for ages 50 and older.

One of the major problems in this study was the complete lack of any data to confirm the self-reported diagnoses of CTD. Given the widely publicized controversy of the health effects of breast implants in the news media, potential bias of overreporting of symptoms among women with breast implants was clearly a major concern. Although Hennekens et al. concluded that the self-reported data "suggest small increased risks of connective-tissue diseases among women with breast implants," they readily admitted that "bias due to differential overreporting of connective-tissue diseases or selective participation by affected women with breast implants remains a plausible alternative explanation." The authors stated that they planned to continue the study by confirming the CTD diagnoses.

Sanchez-Guerrero et al.

This investigation, known as the Nurses Health Study,[19] started in 1976 as a cohort study of nurses from 11 states. The purpose of the study was to evaluate, by use of biennial questionnaires, specific diseases, primarily heart disease and cancer. Approximately 121,000 women were enrolled in the original study in 1976. By 1992, the number of women still alive and participating in the study was 109,750 (90.7%).

The 1992 questionnaire had additional questions to inquire about breast implants and other cosmetic procedures in relationship to specific connective tissue diseases. There were 87,501 women who participated in the 1992 questionnaire; 1,183 had breast implants (876 silicone, 170 saline, 67 double lumen, 14 polyurethane, and 56 unknown). The questionnaire data for breast implants were verified by a sampling technique.

The 5,086 women who reported the following symptoms were sent a follow-up questionnaire designed to elicit further information about symptoms and diseases: rheumatoid arthritis, scleroderma, morphea, systemic lupus, Sjogren's syndrome, arthritis excluding osteoarthritis and fibromyalgia, and connective tissue disease not otherwise defined. The 1,294 women whose answers to the second questionnaire were positive were asked for permission to review medical records. Two rheumatologists, blinded to the implant status, reviewed the medical records for the presence or absence of 41 specific signs and symptoms.

Medical records were located and reviewed for 904 of the 1294 women cited above. Five hundred sixteen of the participants were found to have a recognized CTD. Of these, three (all of whom had rheumatoid arthritis) had breast implants; only one had a silicone breast implant. Of the 904 women whose medical records were reviewed, six had breast implants but only four were silicone breast implants. No cases of scleroderma and breast implants were identified.

McLaughlin et al.

McLaughlin et al.[20] used hospital discharge registry data in Denmark to follow 824 women who had breast implants for cosmetic reasons between 1977 and 1989. Average follow-up was 6.9 years. While the focus of the study was breast cancer, they also looked at CTDs. They reported two cases of scleroderma among the 824 women, a statistically significant finding with the RR of 27.7 (3.1–99.8). In 1995, the researchers issued a retraction,[21] stating that one of the women with scleroderma had a mammary reduction procedure, not a breast implant. Thus, only one woman with breast implant developed scleroderma subsequently, and the revised RR was no longer statistically significant.

Review of Other Investigations

No other specific reports of epidemiologic studies of scleroderma can be found in the literature. Teich Alasia et al.[22] reported no scleroderma among 102 Italian women with breast implants postmastectomy. Duffy and Woods[23] did not find any scleroderma among 274 women who underwent a second breast implant surgery. Giltay et al.[24] did not report any scleroderma cases in the follow-up of 287 breast implant patients. Peters et al.[25] did not report any scleroderma among 500 women with breast implants. Similarly, Schusterman et al.[26] did not find any scleroderma among 250 postmastectomy breast implant patients, and Weisman et al.[27] did not report any scleroderma cases among 125 women with breast implants. In a survey (Wells et al.[28]), no scleroderma was reported among the 222 women with implants who responded. Finally, Muhanna et al.[29] reported that none of the 348 women with scleroderma diagnosed at a scleroderma clinic in Toronto had a breast implant before the diagnosis of scleroderma.

Meta-analysis

Design consideration and statistical procedure

In addition to a qualitative review, we conducted quantitative meta-analyses to summarize the risk estimates from individual studies. In the meta-analsysis, we included only case-control studies.

Case-control studies are the appropriate study design for investigating rare diseases such as scleroderma. Moreover, scleroderma patients in case-control studies were identified through rheumatology practices or hospitals and were diagnosed by rheumatologists. In some prospective studies, the diagnosis was self-reported, and it has been reported that only a small fraction of self-reported diagnoses of CTD met the medical criteria. For example, Star et al.[33] reported that only 21% of self-reported women met the ARC criteria, and Santiago-Young et al.[34] reported that 45% of patients who were self-referred or referred by physicians were diagnosed to have definite or probable rheumatic diseases, compared with 22% among individuals referred by attorneys.

In the case-control studies, information on breast implants was ascertained through questionnaires or interviews, except in the study by Goldman et al.[16], which relied on medical records. Thus, these studies were relatively homogeneous in terms of study design, data source, data instrument, and analytical technique.

Results from these case-control studies are very consistent in that no increased risk of scleroderma was reported. Individually, however, the studies were relatively small, and the statistical power of each was limited. Sample size and statistical power in studying CTD have been discussed,[35] and the advantage of using meta-analysis in investigating rheumatic or connective tissue diseases has been discussed as well.[36,37] Because of the similarity in study design and the consistency in findings, meta-analyses based on these case-control studies were carried out to improve statistical power.

The procedure for the meta-analysis used in summarizing the results from the individual studies has been

Table 1.—*Results (Based on Unmatched Analysis) and Meta-analysis of Case-Control Studies of Breast Implants and Scleroderma*

Study	OR	95% CI
Burns[12]	0.72	0.16–3.32
Englert[13,14]	0.66	0.16–3.86
Hochberg[15]	1.07	0.53–2.13
Meta-analysis	0.94	0.52–1.70

Table 2.—*Results (Based on Matched Analysis) and Meta-analysis of Case Contol Studies of Breast Implants and Scleroderma*

Study	OR	95% CI
Burns[12]	1.30	0.27–6.23
Englert[13,14]	0.52	0.11–2.41
Hochberg[15]	1.11	0.55–2.24
Meta-analysis	1.02	0.56–1.84

described.[30,31] Basically, the pooled risk estimate is the average RR weighted by the reciprocals of the sampling variances of the RR estimates from individual studies on the natural logarithmic scale. Each study is treated as a separate stratum in the meta-analysis, thus preserving the matching, internal comparison, similarity of data source, and data collection between the cases and the controls in each study. This procedure has been demonstrated to be in extremely close agreement with the Mantel-Haenszel method.[32,30] We used the most recent data from any study that had been updated or expanded.

Results

There were three case-control studies specifically for scleroderma: Burns et al.,[12] Englert et al.,[13,14] and Hochberg et al.[15] In addition, Goldman et al.[16] used case-control analyses for a variety of connective tissue diseases, including scleroderma.

We have conducted several meta-analyses of these case-control studies. Because of the zero OR in the Goldman et al. study (no scleroderma cases had breast implants), we have conducted meta-analyses with and without those data.

The unadjusted results of the meta-analyses are presented in Table 1, and the adjusted or matched results, in Table 2. The summary OR for the three case-control studies is 0.94 (0.52–1.70) for the unadjusted analyses and 1.02 (0.56–1.84) for the adjusted analyses, indicating that women with breast implants are not at an increased risk of scleroderma. Furthermore, the combined data have sufficient statistical power to rule out a risk as small as 70%.

If the Goldman et al. study is included by using the OR for all connective tissue disease, then the summary odds ratio becomes 0.84 (0.48–1.48) for the unadjusted analyses and 0.90 (0.51–1.59) for the adjusted analyses. Thus, the inclusion or exclusion of the Goldman et al. data does not change the meta-analysis materially.

Discussion and Conclusions

Meta-analysis can be an effective tool to improve statistical power, provided that such analysis is appropriate for the studies under consideration. If data from more than one study can be combined, the resulting sample size increases. With the increase in sample size, there is a corresponding increase in statistical power. Meta-analyses can be done for both cohort studies and case-control studies. For case-control studies, such statistical procedures are useful when the disease is rare and the exposures are uncommon.

Meta-analyses can provide a properly weighted summary risk estimate and can also consider the consistency of results of the individual studies. Meta-analyses can reduce the subjectivity in comparing different studies in an attempt to understand the current state of knowledge on a particular issue.

The three case-control studies here are quite consistent in study design and data collection. In all three studies, scleroderma patients were systematically ascertained in their respective geographic areas. The controls were identified through systematic randomized procedure. Each study used the ACR criteria for both scleroderma (systemic sclerosis) and CREST, a milder version of the disease. Each study excluded the localized skin disease without systemic effects.

The three case-control studies are also consistent with the other studies, Goldman et al.[16] and the three cohort studies.[17–19] Finally, the cross-sectional assessments by Muhanna et al.[29] is also consistent with the case-control studies.

In the 1980s and early 1990s, the scientific literature reported case reports and case series of women with scleroderma as well as other established connective tissue disease who had breast implants. Based on these case reports, the following question was formulated: Do breast implants cause or lead to the development of scleroderma? The three case-control studies cited in this paper were designed to answer this question. The meta-analysis, by increasing the number of cases and controls, provides a more precise risk estimate and confidence limits than the individual studies.

In summary, neither the case-control studies nor the other epidemiologic data (such as prospective investigations) support the hypothesis that scleroderma is associated with or causally related to breast implants.

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Insulin Signaling

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The following article is another in a series of papers presented at the Annual Meeting of the Western Association of Physicians. The WAP meets in Carmel, usually in the first week of February, along with sister organizations the Western Society for Clinical Investigation and the Western Federation for Clinical Research. These meetings are designed to offer members and guest physicians broad updates in multiple specialties of medicine and basic science. This eclectic approach provides broad cross-fertilization of ideas, often leading to scientific collaboration. Readers of THE WESTERN JOURNAL OF MEDICINE are encouraged to register and attend the meetings. The scheduled program for future meetings will be published in the December issue of the journal.

(Goalstone ML, Draznin B. Insulin signaling. West J Med September; 1997; 167:166–173)

The biological effectiveness of insulin is generally assessed by its ability to regulate levels of glycemia in the blood. Minutes after it is administered, or after it is released endogenously from pancreatic β cells in response to secretagogues, insulin inhibits hepatic glucose production and stimulates peripheral glucose utilization. The resultant decrease in the blood glucose concentration represents the most noticeable and, therapeutically, the most important effect of insulin.

Although insulin's glucose-lowering effect is its most relevant property from a clinical standpoint, it is a pleiotropic hormone that also exerts significant influence on all aspects of carbohydrate, protein, and lipid metabolism. Insulin stimulates amino acid uptake and protein and lipid synthesis, whereas it inhibits lipolysis, proteolysis, and ketogenesis.[1] The question that has puzzled investigators since the discovery of insulin is how one hormone can produce such a plethora of effects not only in different tissues, but also frequently within the same cell. All aspects of insulin action are initiated at the point in time when insulin interacts with its cell-surface receptor.[2,3] Therefore, the key to understanding the mechanism of insulin's pleiotropic action must lie in the insulin signaling network (Figure 1). To understand the specificity of insulin action, one must decipher the maze of signaling pathways that connect the insulin receptor with the enzymes and proteins that carry out insulin's "commands."

The insulin receptor is a heterotetrameric transmembrane protein and is a member of the tyrosine kinase receptor family.[4,5] The tyrosine kinase domain of the insulin receptor is located on the cytoplasmic portion of the β subunit and is activated upon ligand binding. Activation of the tyrosine kinase results in rapid autophosphorylation of several tyrosine residues of the intracellular domain of the β subunit.[6] Subsequently, phosphotyrosyl residues become points of attraction for certain cytoplasmic "effector" proteins. The specificity of interactions between the effector proteins and the

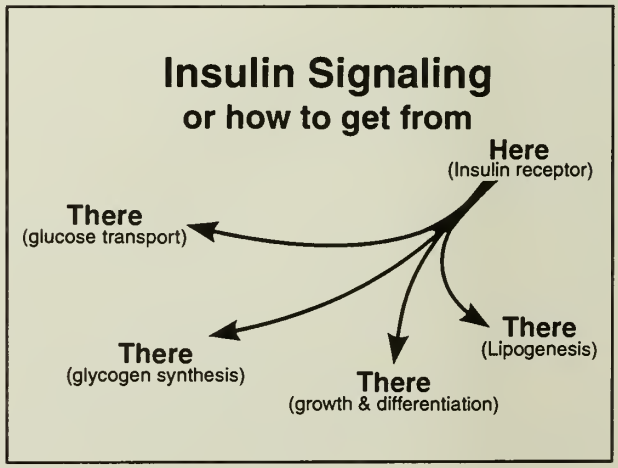

Figure 1.—The insulin signaling system responsible for the pleotropic action of insulin.

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ABBREVIATIONS USED IN TEXT
PI-3 = phosphatidylinositol 3
IRS = insulin receptor substrate

insulin receptor is determined by the particular motif of amino acids adjacent to or surrounding a given tyrosine residue on the β subunit.[7] Interaction between the insulin receptor and the effector proteins, insulin-receptor substrate (IRS-1 and 2) and Shc, results in the phosphorylation of these proteins,[8,9] which in turn promotes attraction and activation of the next layer of insulin-signaling intermediates (Figure 2).

These protein–protein interactions are facilitated by specific, well-conserved domains,[10,11] such as src-homology domains 2 and 3 and the pleckstrin homology and phosphotyrosine-binding domains (Figure 3). These domains allow signaling intermediates to associate and interact with one another, creating a determinate signaling network (Figure 4).

A careful analysis of various interactions among these signaling intermediates reveals that the p85 subunit of phosphatidylinositol 3 (PI-3) kinase is the most "promiscuous" member of the signaling family (Figure 5). It appears to associate with many signaling molecules, although the physiological significance of the majority of these associations remains unclear. Experiments with PI-3 kinase inhibitors and overexpression of the constitutively active catalytic subunit of PI-3 kinase (p110) have demonstrated that this kinase plays an important part in the mechanism of insulin-stimulated glucose transport and DNA synthesis.[12–15]

Despite recent advances in the identification of numerous signaling intermediates, many questions remain unanswered. One of the most important issues is the specificity of insulin's effect. Many growth factors and hormones activate the same signaling intermediates as insulin, but they do not mimic insulin action.[16] A partial explanation of this paradox lies in the expression of isoforms of various intermediates that may respond dif-

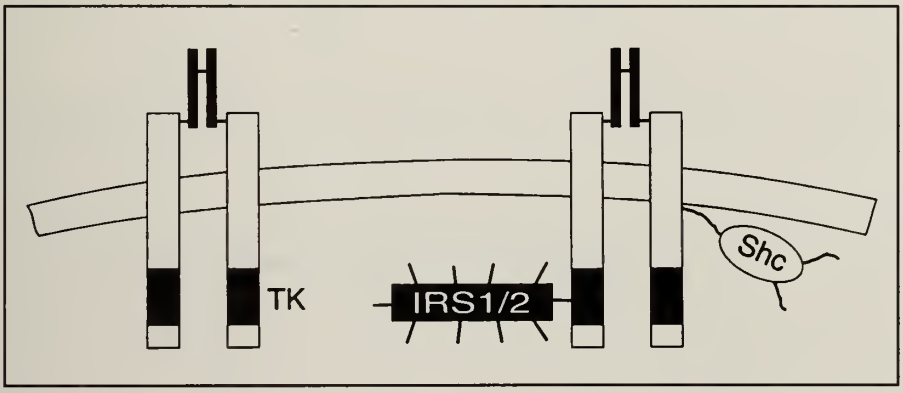

Figure 2.—Interaction of the insulin receptor with IRS-1/2 and Shc, resulting in the phosphorylation of these proteins. TK = tyrosine kinase domain.

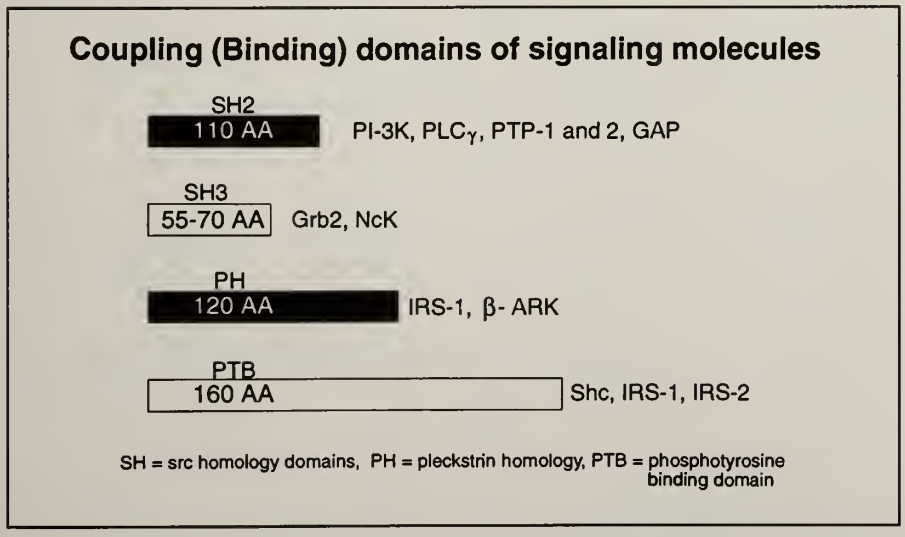

Figure 3.—Coupling domains of different signaling molecules.

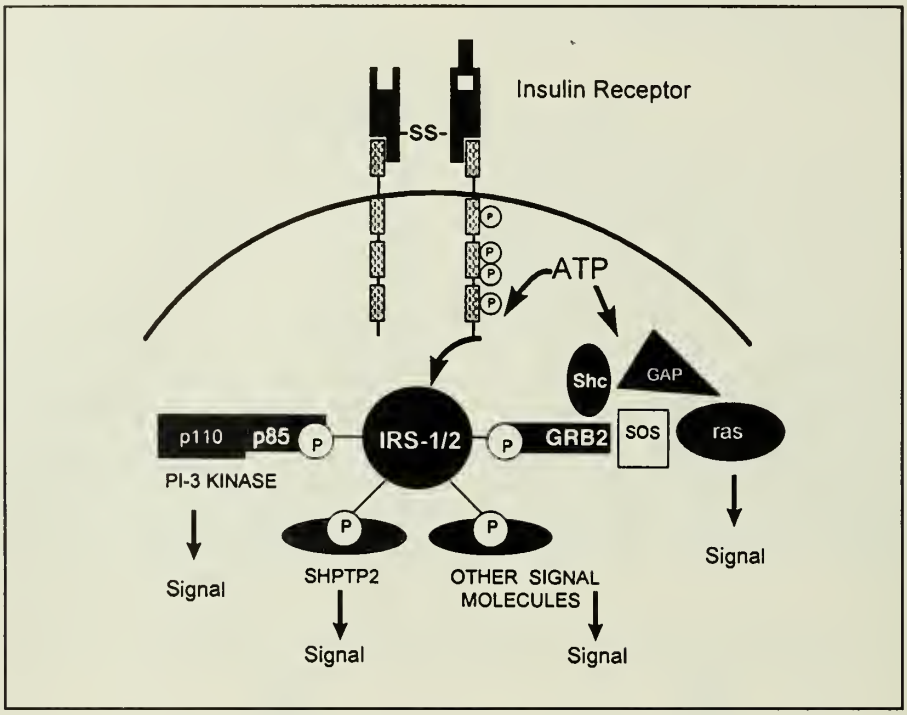

Figure 4.—Recrüitment of effector proteins to IRS-1/2 and Shc in response to the stimulation of the insulin receptor and its tyrosine kinase activity.

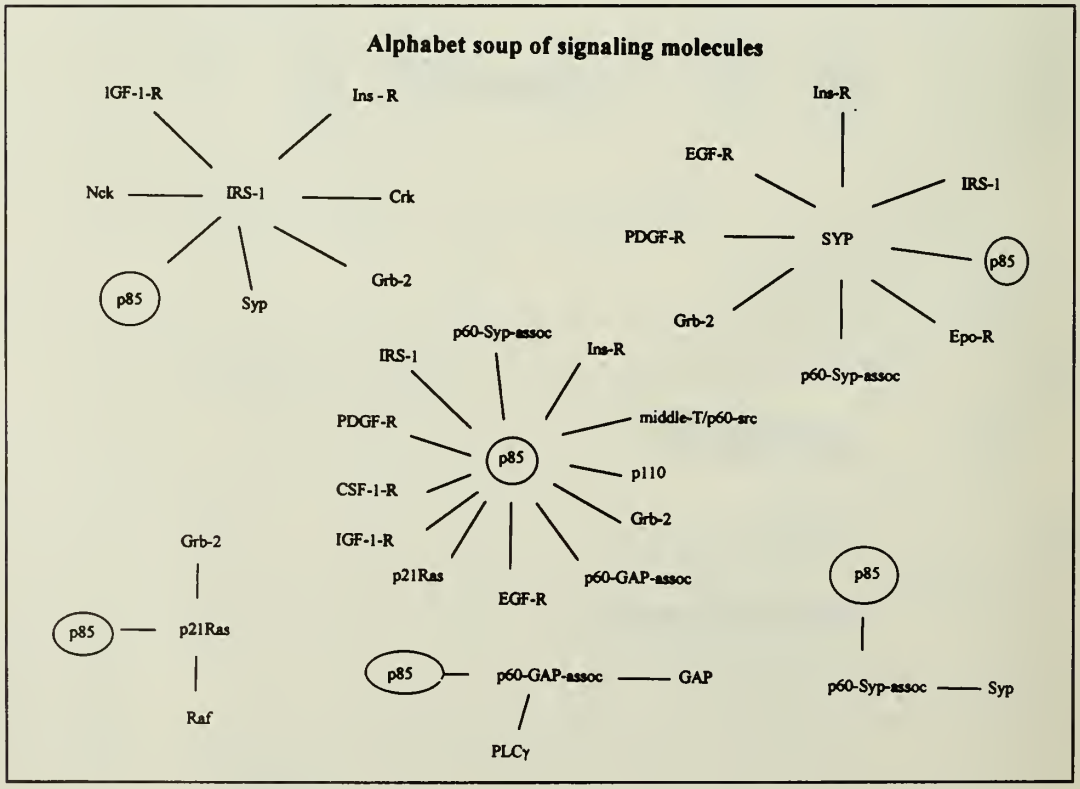

Figure 5.—Associations among various insulin signaling molecules: p85, a regulatory subunit of PI-3 kinase, appears to bind all intermediates and tyrosine kinase–containing receptors. Whether its position in the "insulin universe" is indeed central, remains to be established (from ref. 36, with permission).

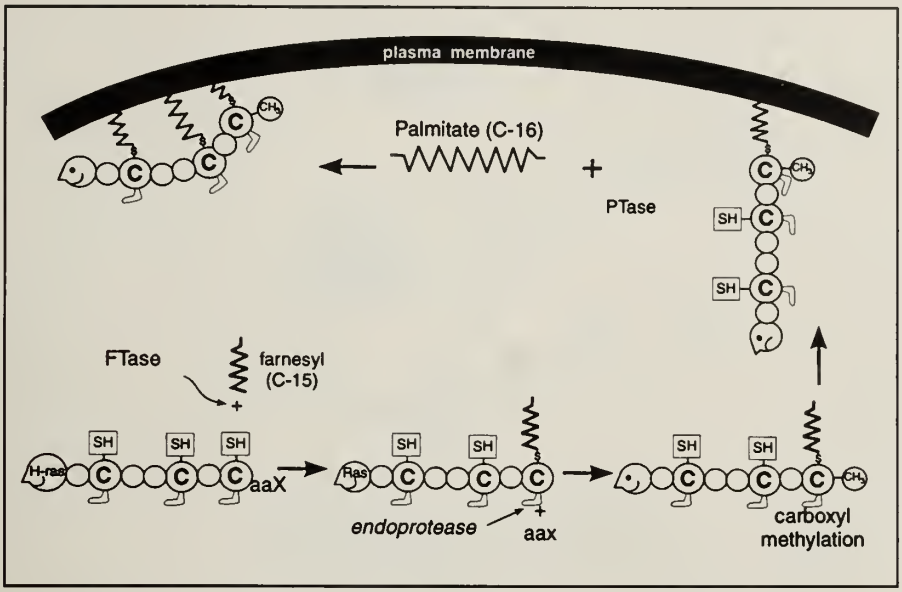

Figure 6.—Posttranslational modification of p21Ras. SH = sulfhydryl group of cysteine (C) residues.

ferently to different growth factors. To date, at least three Raf kinases (Raf A, B, and C), six MEKs, four MAP kinases (ERK I and II, p38, and JNK), and three p85 and two p110 subunits of PI-3 kinase have been identified. Tissue-specific expression of certain isoforms of the signaling intermediates is another variable in the cellular responsiveness of signaling intermediates to insulin and other growth factors. Recently, a specific subcellular location for certain intermediates has been proposed to explain differential cellular responsiveness to insulin and other growth factors. Nave et al.[17] demonstrated that both insulin and PDGF activate PI-3 kinase. Although both hormones activate the plasma membrane–associated enzyme, only insulin significantly stimulates the microsome-associated PI-3 kinase,[17] a fraction enriched with the GLUT-4–containing vesicles.

In recent years, numerous signaling intermediates have been identified, characterized, and cloned. Nevertheless, despite significant advances in understanding the mechanism of insulin signaling, the precise relationship of these signaling molecules to the final biological manifestations of insulin action remains enigmatic. As mentioned above, to date only the activation of PI-3 kinase has been implicated in the mechanism of insulin's effect on glucose uptake.[12–15,18–21] The ways in which other intermediates signal metabolic aspects of insulin action are unknown. Experimental evidence, however, strongly indicates that the Ras-MAP kinase pathway is not involved in mediating insulin effects on glucose transport, lipogenesis, inhibition of lipolysis, inhibition of *PEPCK* gene expression, stimulation of glycogen synthesis, amino acid uptake, or PHAS-1 phosphorylation.[22] In contrast, the Ras-MAP kinase pathway appears to be extremely important in mediating effects on the cell nuclei of insulin and other growth factors.

Insulin is a very potent activator of Ras, significantly increasing the loading of p21Ras with GTP.[23–25] Activation of p21Ras is facilitated by the guanine nucleotide exchange activity of Sos, another downstream effector of the insulin signal pathway.[26] After insulin binding, autophosphorylation of the insulin receptor, and phosphorylation of IRS-1 and Shc, Sos associates with IRS-1 and Shc via its companion Grb-2.[27] Once activated, Sos promotes the dissociation of GDP from p21Ras·GDP (the inactive conformation of p21Ras) and allows binding of p21Ras with GTP to form p21·GTP (the active conformation of p21Ras). Whereas this process is potentiated by insulin,[28] it is the GTPase-activating protein, glial acidic protein (GAP), that hydrolyzes the p21Ras-bound GTP into GDP and reverts p21Ras into its inactive form.

Recent studies have determined that only membrane-associated p21Ras can be activated by Sos and deactivated by GAP.[29,30] The attachment of p21Ras to the plasma membrane is a process that consists of three steps.[31–33] The first step that commits p21Ras to the plasma membrane is the farnesylation of the Ras protein. A molecule of farnesyl is attached to cysteine 186, an animo acid residue that is found at the C-terminal domain of Ras and is part of the CaaX motif. The next step is the proteolytic cleavage of the aaX tail of Ras. The final step is the carboxymethylation of the farnesylated cysteine 186 residue. Farnesylated and carboxymethylated p21Ras is then translocated to, and anchored at, the plasma membrane. Subsequent palmitoylation of p21Ras solidifies its attachment to the membrane (Figure 6). Farnesyl that is attached to p21Ras is

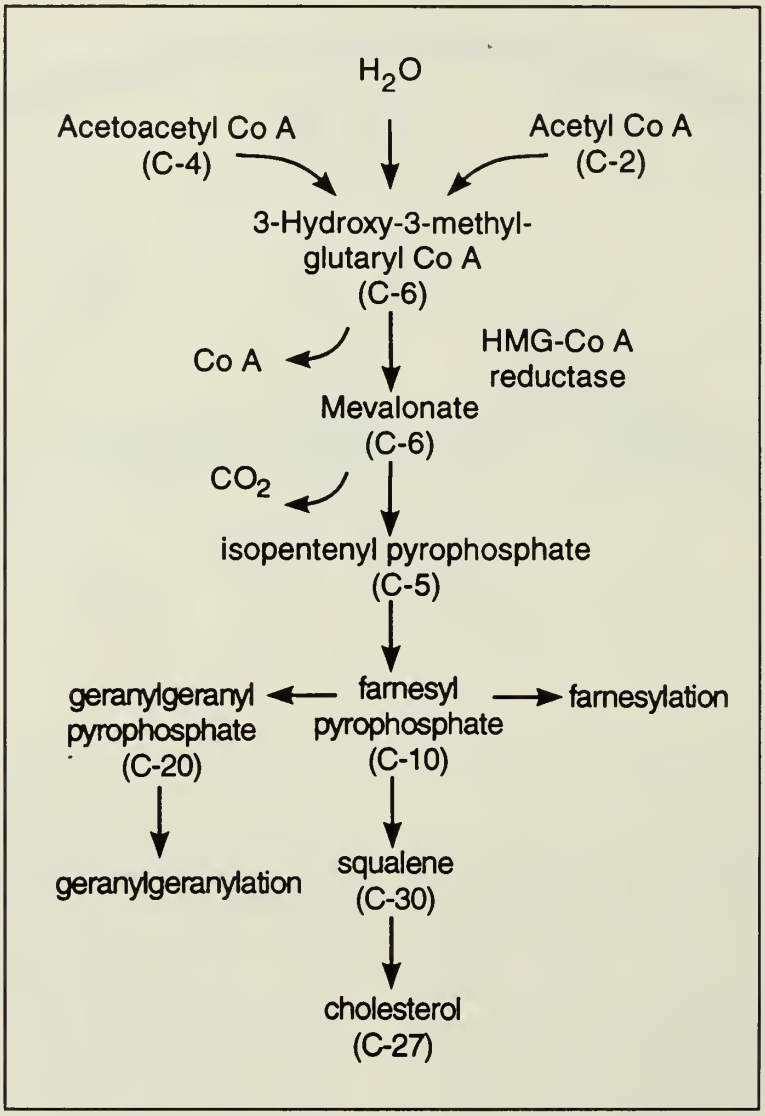

Figure 7.—Production of farnesyl in the process of cholesterol synthesis.

generated in the process of cholesterol synthesis (Figure 7). Although the majority of newly synthesized farnesyl is used to manufacture cholesterol, small amounts of this lipid are transferred to the CaaX-containing proteins by the ubiquitous enzyme, farnesyltransferase (FTase).

FTase consists of two subunits, α and β.[32,33] The role of the α subunit is not well understood, but it appears to promote the stabilization of the enzyme-protein-lipid complex (Figure 8). Interestingly, the α subunit of FTase is identical to the α subunit of another lipid-transferring enzyme, geranylgeranyl transferase 1 (GGTase-1). The β subunit, however, appears to bind both the lipid moiety (farnesyl) and the CaaX-containing protein, providing these proteins with substrate specificity. The β subunit of FTase binds proteins that contain serine, methionine, or glutamine in the X position of the CaaX box. These proteins include Ras, nuclear lamins A and B, the γ subunit of transducin, and peroxisomal protein PxF.

The activity of FTase can be assessed by three methods. First, using an in vitro assay, one can determine the ability of cell lysates (sources of enzymes) to promote the association of ^{3}H-farnesyl pyrophosphate with bacterially expressed p21Ras. Second, FTase activity can be assessed in vivo by determining the amounts of ^{3}H-mevalonic acid (precursor of farnesyl) that are incorporated into endogenous p21Ras. Finally, one can measure the amounts of farnesylated and unfarnesylated p21Ras in the cell lysates that appear after exposure of these cells to various growth factors. Separation of the farnesylated p21Ras from the unfarnesylated p21Ras is achieved by the extraction of the cell lysate with Triton X-114. This detergent extracts the lipophilic, farnesylated Ras into the detergent phase and separates it from the unfarnesylated p21Ras, which remains in the aqueous

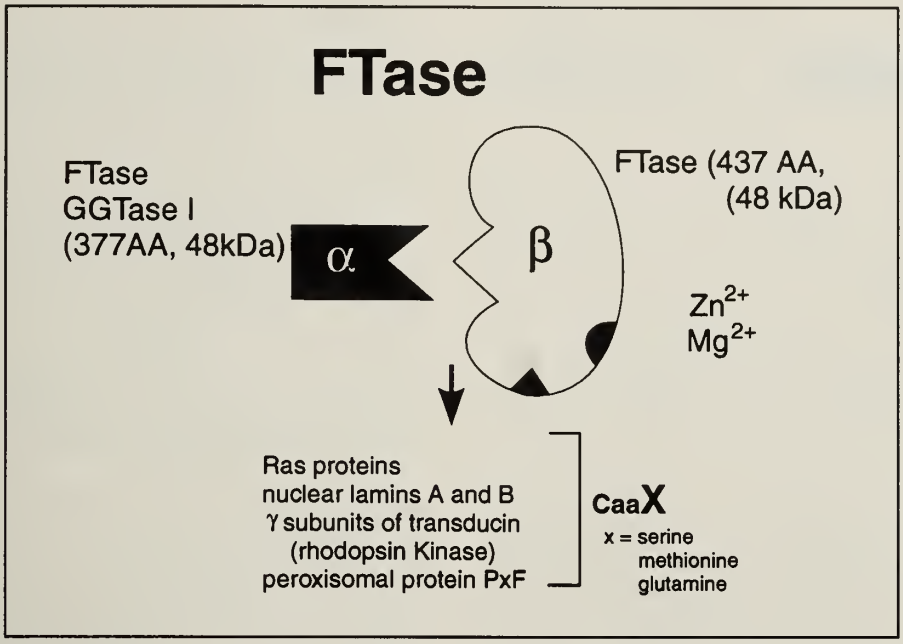

Figure 8.—Structure of FTase: α and β subunits (number of amino acid residues and molecular weights are in parentheses) as well as substrates of FTase. The α subunit of FTase is shared with geranylgeranyl transferase I (GGTase I).

phase. Ras proteins are then immunoprecipitated from both phases and determined by Western blotting.

Using all three methods, we recently demonstrated that insulin activates FTase in adipocytes, fibroblasts, and vascular smooth-muscle cells in a time- and dose-dependent manner (Figure 9).[34] Subsequent experiments have revealed that insulin promotes the phosphorylation of the α subunit of FTase (Figure 10) and that the degree of phosphorylation correlates with the enzymatic activity of FTase (Goalstone, Carel, Leitner, and Draznin, unpublished data). The net result of insulin-induced stimulation of FTase is a significant increase in the amount of membrane-associated farnesylated p21Ras that can be activated by other growth factors. Because

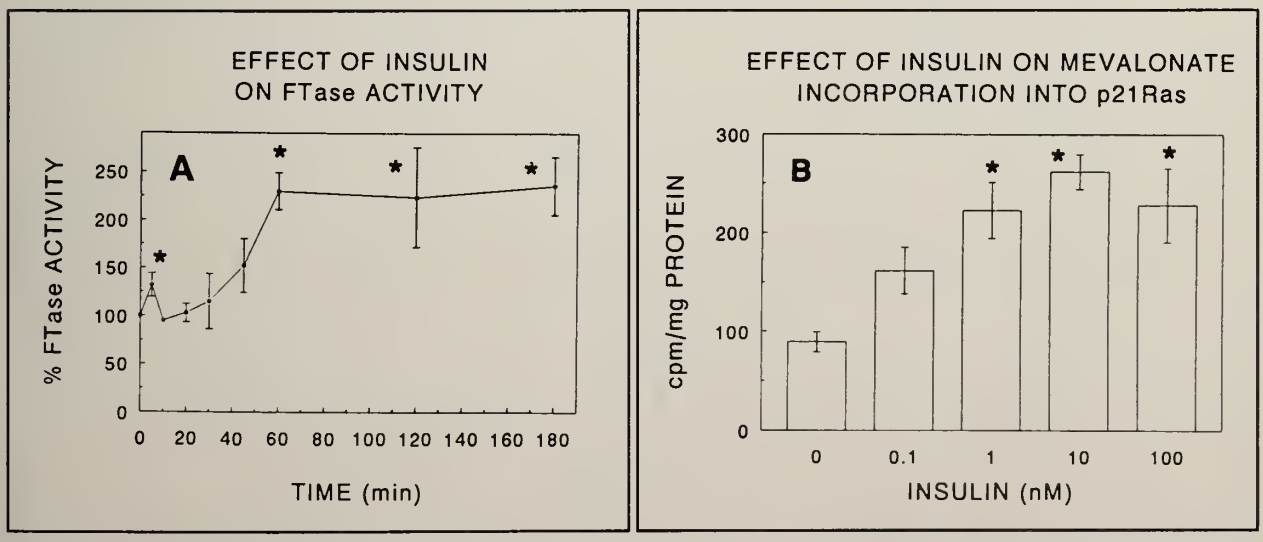

Figure 9.—Effect of insulin on FTase activity: the time course (A, in vitro assay) and the dose response (B, in vivo assay). *$P < 0.05$ vs control (from ref. 34, with permission).

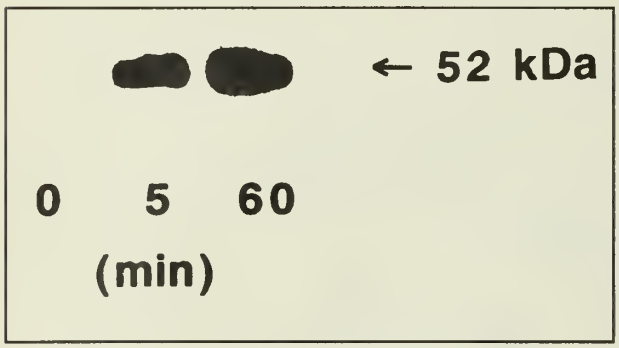

Figure 10.—Phosphorylation of the α subunit of FTase (52 kDa) after the exposure of cells to insulin (100 nM) for 5 or 60 minutes.

greater amounts of farnesylated p21Ras are available at the plasma membrane for activation, the exposure of cells to insulin can result in the augmentation of the mitogenic cellular responses to other growth factors (Figure 11). We have therefore hypothesized that the detrimental influence of hyperinsulinemia may be related to the effects of insulin on the cellular pool of farnesylated p21Ras.[35]

Conclusions

If the mechanism of insulin signaling is a large jigsaw puzzle, many pieces have been found, identified, and well characterized. The remaining task is to assemble these pieces and to discover the missing links. Particularly important and difficult parts of the puzzle are metabolic vs mitogenic signaling, tissue specificity, and the specific action of insulin signaling. Solving this puzzle will not only help uncover the mechanism of insulin action, but may also help prevent the detrimental influence of hyperinsulinemia.

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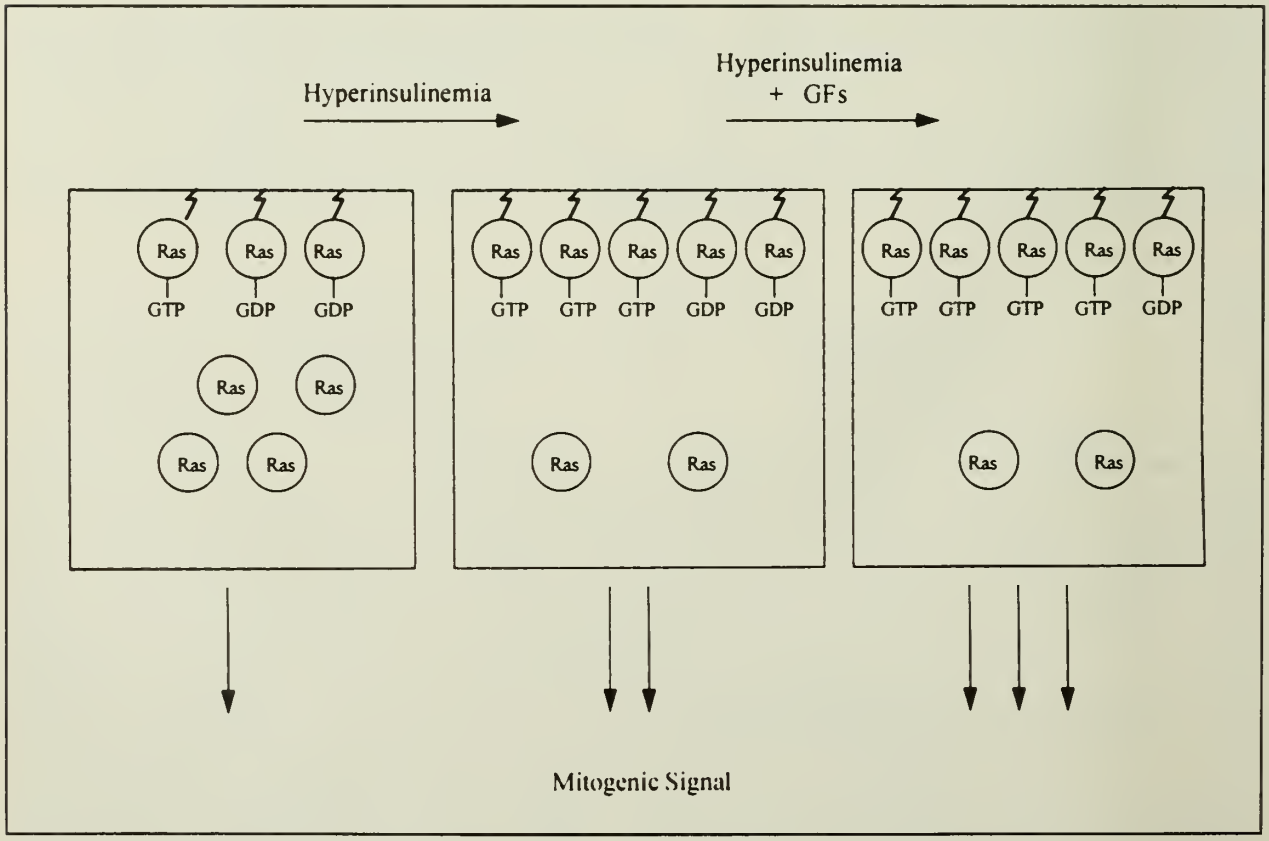

Figure 11.—Proposed model of the potentiation by insulin of the cellular mitogenic response to growth factors (GFs) (from ref. 35, with permission).

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Epitomes

Important Advances in Clinical Medicine

Family and General Practice

Jan O. Sonander, MD, and Daljeet S. Rai, MD, Section Editors

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in family and general practice. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in family and general practice that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Family and General Practice of the California Medical Association, and the summaries were prepared under the direction of Drs Sonander and Rai and the Panel.

Advances in Dementia Management

Dementia is a syndrome of progressive cognitive and functional decline that affects 5–10% of the US population aged 65 and older. Its incidence doubles every 5 years after age 65.

Clinicians often underestimate the amount of impairment that older patients experience in daily living. Only about one half of patients with dementia are identified by primary care physicians using the routine history and physical examiniations. Early recognition of dementia may allow for treatment of reversible causes, amelioration of partially reversible causes, and delay of functional disability for some irreversible causes of dementia. Approximately 10–15% of cognitive impairment in older adults is due to treatable conditions such as hypothyroidism and drug toxicity. Early identification of patients with dementia allows the patient and family to plan for future long-term-care services, and to take the opportunity to participate in trials of new, potentially helpful therapies. Unrecognized dementia may result in inappropriate use of emergency services and unneeded patient/family discomfort.

The Agency for Health Care Policy Research (AHCPR) recently issued clinical practice guidelines to assist health care professionals in the early and accurate identification of Alzheimer's disease, the most common cause of dementia. Because dementia is often misdiagnosed or unrecognized in its early stages, the guidelines identify early symptoms and signs of dementia, guiding early assessment. Certain symptoms, such as problems with spatial ability and orientation or difficulties in learning, language, and handling complex tasks, distinguish early-stage dementia from normal aging and from other syndromes that affect cognition such as depression or delirium. These triggers prompt early assessment such as focused history, physical, functional, and mental status assessment. Using these decision support guidelines, primary care clinicians may identify the cause of dementia with greater accuracy.

Specific identification of Alzheimer's disease allows early treatment with newer agents that may better control behavioral signs and symptoms, improve cognitive function, and slow disease progression. Patients suffering from dementia commonly suffer from behavioral symptoms such as depression, anxiety, psychosis, aggression, agitation, and apathy. More effective medications are now available for the treatment of these conditions resulting from expanded Medicaid formulary inclusion of existing effective agents (such as serotonin reuptake inhibitors, SSRIs), the recognition that antiepileptic drugs have utility in behavior management (carbamazepine, valproic acid), and the introduction of newer psychotropics with fewer side effects (respiradol, olanzepine).

Therapies thought to enhance cognitive function in Alzheimer's disease by restoring functional deficits in neurotransmission, increasing cholinergic transmission, are available. Two cholinesterase inhibitors (tetrahydroaminoacridine and donepezil) show promise, both of which have been approved by the Food and Drug Administration. The use of each has demonstrated significant improvements in cognition and function, delaying suffering and costly use of long-term-care resources. There is modest evidence to support the benefit of selegiline, a monoamine oxidase inhibitor, and Vitamin E, which have been shown to cause mild improvement in cognitive function and behavior.

It is crucial that clinicians carefully evaluate patients with suspected dementia, obtaining information from informants, perform appropriate laboratory and imaging tests, and render a specific dementia diagnosis. Patients

should then be monitored for intercurrent medical problems, which frequently present as a worsening of dementia symptoms. Such problems should be treated, and dementia symptoms monitored. Improving sensory input can result in diminishing dementia symptoms and improved function. Environmental modification such as improving lighting, decreasing noise levels, and controlling wandering while promoting environmental exploration may lead to improved function. Clinicians can ease exhaustion and conflicts by teaching patients, families, and caregivers about available community resources that can help with coping with the illness and planning long-term-care services. These include Area Agency on Aging (in-home and community services; nutrition), Alzheimer's Disease Centers (clinical services; research and education), and the Alzheimer's Association (education; support groups; adult day care; respite).

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Treatment for Human Immunodeficiency Virus (HIV) Infection

As recently as 1993 and the International AIDS Conference in Berlin, the future of HIV antiretroviral therapy had darkened to a depressing gray. The Concorde Study questioned the long-term value of zidovudine (AZT) monotherapy for asymptomatic individuals, while other studies involving people with advanced disease found minimal benefit from switching to, or adding another, antiretroviral therapy. In the last 4 years, however, antiretroviral therapy has experienced a revival. Plasma HIV RNA testing allows close monitoring of HIV therapy, which has become more effective with the development of a more potent class of antiretrovirals, protease inhibitors. After years of being in desperately short supply, hope can again be found within offices of physicians treating HIV disease.

Multiple studies have demonstrated the predictive value of plasma HIV RNA levels, commonly referred to as "viral loads." This testing measures the amount of ongoing HIV replication, which correlates with the rate of CD4 cell destruction. In contrast to CD4 testing—a static measure of immune system damage—this test is a dynamic marker predicting the risk of future damage and, therefore, disease progression. Perhaps the most valuable role of HIV RNA testing, when used along with CD4 testing, is to help individualize the starting and changing of a patient's antiretroviral regimen.

Recent developments in antiretroviral drugs have also been dramatic. As of the Berlin Conference, only four drugs (zidovudine, didanosine, zalcitabine, and stavudine) were readily available, and all four were in the same class (nucleoside reverse transcriptase inhibitors). At present, 11 antiretrovirals have been approved by the Food and Drug Administration, including a new nucleoside (lamivudine) and six drugs in two new categories. Saquinavir, ritonavir, indinavir, and nelfinavir are protease inhibitors, which act on protease, another enzyme essential to the HIV life cycle. Nevirapine and delavirdine are non-nucleoside reverse transcriptase inhibitors (NNRTIs), which inhibit reverse transcriptase, but have a different chemical structure than nucleosides. Protease inhibitors are potent, having a monotherapy capacity to reduce viral load by 1- to 2-log; other drugs typically yield only a 0.5- to 1-log reduction.

Generally, a protease inhibitor is used in combination with at least two other drugs—a mode of treatment dubbed "highly active antiretroviral therapy" (HAART). The goal of HAART is to reduce plasma HIV RNA assays to below a detectable level (around 100–500 copies/ml, depending on technology used). The short-term benefit of HAART has been well demonstrated, perhaps most dramatically in a ritonavir study that found a survival advantage for people with advanced disease randomized to receive ritonavir along with whatever drugs they were receiving. Pending further research, long-term clinical benefit remains largely theoretical. Two advantages of prolonged suppression of HIV are anticipated. A dramatic reduction in the rate of CD4 cell destruction should lead to a marked slowing in HIV progression, and the synergistic activity of a multiple-drug regimen should significantly delay the development of drug resistance.

Now more than ever, drug resistance is a major concern. At one extreme of antiretroviral potency—the absence of any drug therapy—HIV will not experience the selective pressure that leads to resistance. At the other extreme—a highly potent therapy that suppresses HIV to undetectable levels—mutation to a resistant strain is dramatically slowed. The risk of resistance is greatest when potency is intermediate, when a regimen uses weaker drugs or is prescribed in insufficient doses, or because a person intermittently misses doses, leading to prolonged troughs in drug serum levels.

To address this last concern, the primary care physician can foster patient compliance in several ways: 1) evaluating each person's ability to adhere to a given regimen; 2) pretreating substance abuse and social instability; 3) educating about a new regimen (including a detailed schedule of dosing including food and water restrictions, and information about drug interactions and toxicities); and 4) suggesting strategies that will support adherence (a pillbox, a note on the bathroom mirror or refrigerator, an alarm-watch, extra supplies of medications at places fre-

quently visited, enlisting support from friends).

The selection of a given regimen should combine a knowledge of a person's antiretroviral history (including the effect of drugs on CD4 and viral load counts, toxicities, and the likelihood of resistance) with plans about what to do if the regimen fails. This increasingly complex task has been reviewed recently by two panels: one convened by the National Institutes of Health, focusing on principles of therapy; the other by the Department of Health and Human Services and the Henry J. Kaiser Family Foundation, offering more concrete guidelines for antiretroviral prescription. The complexity of these documents supports a growing consensus that antiretroviral management should be done by physicians with considerable HIV experience or by primary care doctors who consult frequently with a specialist.

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Advances in Diabetes Management

DIABETES IS A COMMON yet complex set of medical conditions unified by high plasma glucose. It can result from insulin deficiency, insulin resistance, or both. Advances in both the diagnosis and treatment of diabetes have revolutionized the disease over the past few years. These advances come from a new conceptualization of the disease, clinical trial data, and the development of new treatments. These advances have put diabetes at the forefront of quality assurance efforts.

The recent report from the American Diabetes Association's Expert Committee on the Diagnosis and Classification of Diabetes Mellitus presents several advances. Perhaps the most important is an adjustment of the diagnosis of diabetes, specifically the lowering of the fasting plasma glucose level needed to make the diagnosis. In order to have diagnostic criteria be more internally consistent, the new criteria state that diabetes should be diagnosed if a person has a fasting plasma glucose ≥126 mg/dl (7.0 mmol/l) or a 2-hour plasma glucose ≥200 mg/dl during an oral glucose tolerance test or a glucose measurement ≥200 mg/dl in a person with symptoms. The committee's recommendation against universal screening for gestational diabetes (and in favor of more selective screening) has met with general enthusiasm, while the recommendation to consider screening all adults over 45 years old had mixed reviews.

Treatment advances have come from two sources, one philosophical, the other based on specific drug use. First, the landmark Diabetes Control and Complications Trial (DCCT) trial confirmed that aggressive management of blood glucose leads to a reduction in diabetic microvascular complications (nephropathy, neuropathy, and retinopathy.) The trial's findings are limited by the young age of the participants (too young to measure cardiovascular outcomes, thus leaving the potential benefits of glycemic control on cardiovascular endpoints an unresolved question) and the difficulty of translating the results—performed on patients with type 1 diabetes—to those with the more common type 2 diabetes. Still, most clinicians take the DCCT results as an indication to push for tighter control of blood glucose in diabetic patients.

Therapeutic advances include new uses for old medications (such as bedtime NPH insulin) as well as new formulations. Oral hypoglycemic agents are achieving increased success with the introduction of second-generation sulfonylureas, biguanides, α-glucosidase inhibitors, and troglitazone. The α-glucosidase inhibitors exert their activity in the gastrointestinal tract by reversibly inhibiting the enzymatic cleavage of complex carbohydrates to simple absorbable sugars. An α-glucosidase inhibitor may be given as monotherapy with diet or in combination with diet and a sulfonylurea drug. Troglitazone is another new oral agent unrelated to sulfonylureas, biguanides, and α-glucosidase inhibitors. Troglitazone increases the body's sensitivity to insulin. When used in patients with type 2 diabetes, troglitazone not only decreases fasting blood glucose but also favorably affects the patients' lipid profile and lowers plasma insulin levels, both changes likely to improve cardiovascular risk.

Monitoring the care provided to patients with diabetes can provide insights into quality of care issues. National groups such as the National Committee for Quality Assurance (NCQA), with its Health Plan Employer Data and Information Set (HEDIS) assessment, and the Foundation for Accountability (FACCT) have focused on diabetes. For example, the current HEDIS 3.0 evaluates how frequently patients with diabetes receive eye exams, with other measures being tested for possible inclusion in the future. FACCT's list of quality measures in diabetes is even more extensive.

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Bisphosphonates in the Treatment of Osteoporosis

OSTEOPOROSIS, A BONE DISEASE characterized by low bone density and micro-architectural deterioration, causes 1.3 million fractures annually. Each year, osteoporotic hip fractures alone are responsible for almost 30,000 deaths, an estimated 1,300,000 home health care visits, and nearly 33,000,000 nursing home days. Collectively, osteoporotic fractures cost the nation more than $13 billion.

Epidemiologically, osteoporosis affects those over 65 years of age, the fastest-growing segment of our population. In 1980, 11% of Americans were over 65. The percentage is now nearing 14 and is expected to double by 2050. Clearly, the need for safe, effective therapy is high.

Bone resorption followed by bone formation are the sequential metabolic events that make up the bone-remodeling cycle. In the first three decades of life, total body bone mass increases because more bone is formed during each remodeling cycle than is resorbed. By the middle of the fourth decade of life, resorption outpaces formation and bone mass gradually declines.

Current pharmacologic therapy to treat osteoporosis reduces bone resorption. The three classes of drugs categorized as antiresorptive agents are estrogens, calcitonin, and bisphosphonates.

The bisphosphonates, formerly called diphosphonates, are compounds composed of two phosphate groups attached to a central carbon atom. The mechanism by which bisphosphonates inhibit bone resorption is incompletely understood. Some evidence suggests a direct disruption of the osteoclasts' intracellular structures leading to diminished metabolic activity and perhaps cell death. Other studies support an interruption in the differentiation of the osteoclast precursor to mature osteoclast.

Regardless, decreased bone resorption is detectable within days of an oral administration. This allows bone formation to occur without bone resorption, resulting in a net acquisition of bone. However, this uncoupling of formation from resorption is not indefinite and a new equilibrium is achieved, albeit at an overall lower level of bone turnover. While current evidence suggests that bisphosphonate-treated bone can appropriately remodel, repair damage, and heal fractures, more data will be needed before their long-term safety is demonstrated.

Gastrointestinal absorption of bisphosphonates is poor, mandating taking the medication on an empty stomach and with tap water only. What little drug is absorbed is cleared from the plasma within 6 hours. Nearly 50% of the absorbed amount is bound to bone. Within this compartment, bisphosphonates remain for prolonged periods; the half-life of alendronate is calculated to exceed 10 years.

The beneficial effect of orally administered bisphosphonates on bone mineral density has been firmly established. Placebo-controlled double-blind studies of intermittent cyclical etidronate treatment of postmenopausal women demonstrated an approximate 5% gain in lumbar bone mineral density. Most of the gain was achieved in the first year, but extension studies have confirmed additional slight increments in bone mineral density. Etridonate was given orally for only the first 2 weeks of each 3-month period, since prolonged daily administration of etidronate causes osteomalacia.

Pamidronate, about 10-fold as potent as etridonate at inhibiting bone resorption but available in this country only for intravenous administration, has been shown to increase bone mineral density of the lumbar spine and femoral trochanter by 7 and 5.4%, respectively, following 2 years of daily, oral administration.

Two large studies comparing daily alendronate (about 500- to 1000-fold more potent than etidronate) with placebo have recently been published. In one study, 2,027 postmenopausal, osteoporotic women with at least one vertebral fracture were randomly assigned to receive alendronate, 5 mg daily for 2 years followed by 10 mg daily for 1 year, or placebo. After 3 years, the alendronate group showed a significant increase of femoral neck, total hip, and lumbar spine bone mineral density of 4.1, 4.7, and 6.2%, respectively, over the placebo control. Another study randomized 478 postmenopausal women with osteoporosis to placebo or three alendronate regimens. After 3 years, the 10 mg per day alendronate group increased bone mineral density at the lumbar spine, femoral neck, and femoral trochanter 9.6, 4.7, and 7.4%, respectively, over the placebo group.

Although demonstrating increased bone mineral density is valuable, the real litmus test of clinical efficacy is fracture reduction. The data is not overwhelming, but estrogen therapy is generally believed capable of significantly decreasing the incidence of hip fracture. Only one study is large enough and designed to specifically evaluate the effect of a bisphosphonate on fracture evidence. Mentioned above, this study of 2,027 postmenopausal osteoporotic women demonstrated reduction of fracture incidence at vertebra, hip, and wrist of 46, 51, and 44%, respectively, in the alendronate-treated group compared with the placebo-treated group.

But gains may come at a price. Aside from inducing osteomalacia, etidronate may cause gastrointestinal problems in a small percentage of patients. The aminobisphosphonates are capable of causing more severe gastrointestinal side effects but do not cause osteomalacia. Of greatest concern is their capacity to induce esophageal lesions. A recent report identified three patients with severe esophagitis from alendronate (an aminobisphosphonate).

The bisphosphonates are an important class of drugs for treating postmenopausal osteoporosis. Although drugs within this class differ from one another, they have proven capacity to increase bone mineral density, and one agent (alendronate) reduces fracture incidence. In this country, two compounds are available for oral administration: etidronate is taken intermittently, 400 mg per day for 2 weeks followed by 11 weeks of treatment with calcium and vitamin D. Alendronate is dosed daily at 10 mg and taken on an empty stomach with tap

water. To reduce the risk of esophageal damage, it should be taken with at least 6 to 8 ounces of water and the patient must remain upright for at least 30 minutes and until the first meal of the day has been eaten.

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Obesity as a Chronic Disease

OBESITY IS USUALLY CONSIDERED a lifestyle disease. Those who are morbidly overweight are often regarded as weak in character or lacking discipline. Judgmental attitudes against the obese are pervasive in society and are just as harmful as other forms of social prejudice.

Obesity should be recognized as an important chronic disease, much like hypertension, hyperlipidemia, and type 2 diabetes. Like those diseases, obesity is a complex interplay of genetic, metabolic, and psychosocial factors.

The importance of obesity has been recently clarified. While more than 400,000 premature deaths per year in the US are attributed to smoking, overeating and lack of physical activity come in at a close second, accounting for 300,000 premature deaths per year. In the past, obesity without other co-morbidities has been considered a relatively benign condition. The physiology of being overweight, however, directly contributes to elevated blood pressure, hyperglycemia, and a high-risk lipid profile.

Like other complex chronic diseases, the management of obesity requires a multidisciplinary program, combing lifestyle modifications with the possibility of pharmacotherapy. A team approach, extensive patient education, and regular long-term follow-up are hallmarks of therapy.

The goal in treating obesity is to achieve a healthier weight, not the elusive ideal weight. A 10% reduction in weight may result in dramatic improvement in co-morbidities such as elevated blood pressure, hyperglycemia, and lipid disorder. The best objective measure ofobesity is the body mass index (BMI), which is calculated using height and weight (tables for calculating BMI are now readily available). A BMI of 27 or greater indicates obesity.

Greatly reducing the fat content of the diet is often successful in treating obesity. Vegetarian diets alone may not be successful if they contain an abundance of oils. All dietary fat is high in calories (9 calories per gram), and weight loss usually occurs if calories from fat make up less than 20% of total calories. The nutritional approach to obesity is directed toward reducing both fat content and total calories in the diet.

Increasing physical activity is the second cornerstone of management. Heavy exercise may be dangerous for obese patients, but the addition of regular physical activity, such as walking, to the daily routine fosters weight loss. Both the dietary and physical activity components of the treatment must be incorporated into the patient's lifestyle for long-term success. Behavior modification is focused on the long term rather than temporary changes.

Pharmacotherapy for the obese has entered mainstream therapy. Centrally acting drugs focusing on the neurotransmitters norepinephrine and serotonin and avoiding the dopinergic effects of amphetamines have been found to be relatively safe and effective. A combination of phentermine, a norepinephrine-releasing agent, and fenfluramine, a serotonin-releasing agent and reuptake inhibitor, has become popular. Concerns about an increase in primary pulmonary hypertension and, more recently, cardiac valvular defects have raised important questions regarding the long-term safety of these drugs. New agents, such as sibutramine, which is not a releasing agent but rather a norepinephrine- and serotonin- reuptake inhibitor, may be safer. Other therapeutic agents, such as Orlistat, which acts directly on the intestine to reduce the absorption of fat, provide an alternative approach to therapy.

If we accept the serious morbidity of obesity, long-term therapy including drugs, if necessary, should be considered standard medical therapy. Currently, many health plans do not cover anti-obesity treatment. This is partly due to the popularity of such treatment for cosmetic concerns. It is important that all of medicine recognize the seriousness of obesity and accept the importance of therapy. Using the BMI as a diagnostic standard should clarify those persons who require therapy. Just like hypertension, hyperlipidemia, and type 2 diabetes, obesity is a chronic disease and must be aggressively managed.

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Alerts, Notices, and Case Reports

Subarachnoid Hemorrhage at High Altitude

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RAPID ASCENT TO ALTITUDES over 2500 meters can result in acute mountain sickness (AMS). AMS may progress to severe forms of altitude illness, including that known as high-altitude cerebral edema (HACE) with symptoms of severe headache, vomiting, ataxia, confusion, localized paralysis, coma, and death.[1] With timely descent, the syndrome resolves. Severe neurologic impairment presenting at altitude is usually attributed to HACE, but other acute life-threatening neurologic illnesses need to be considered.

Neurologic symptoms at high altitude that persist after descent have been associated with drug-induced hypoglycemia,[2] brain tumors,[3] migraine with aura,[4] transient ischemic attacks,[5] and cerebral infarction.[6] Subarachnoid hemorrhage (SAH) presenting at high altitude has been previously noted in an autopsy series of seven altitude-related deaths.[7] To our knowledge, there is no other mention in the medical literature of SAH occurring under these circumstances. We report a case of SAH following recent ascent to high altitude.

Report of a Case

A previously healthy 72-year-old retired forest worker flew from Sweden to Kathmandu (elevation 1400 meters) in preparation for a trek in the Mt. Everest region of Nepal. After staying in Kathmandu for 3 nights, the patient flew to 2900 meters and hiked to an altitude of 4700 meters over the next 9 days. On day 2, after ascending to 3400 meters, he experienced mild frontal headache and weakness. Suspecting mild AMS, he chose to delay any further ascent for 4 nights until symptoms completely resolved. The patient remained symptom-free through the remainder of his climb to 4700 meters.

After 2 nights at 4700 meters, the patient descended to 4200 meters, at which point one of the authors noted that he appeared remarkably well given his age, and the patient reported feeling better than at any other time during his expedition at high altitude. At 6 a.m. the following day, the patient reported that he had been awakened suddenly by a severe occipital headache, although he had otherwise slept well. He took two paracetamol tablets and remained in bed. An hour later, the patient was found to be unresponsive by a companion. One of the authors residing at the nearby clinic was urgently summoned.

The patient was lying in bed and unresponsive to stimuli. His pulse was 118 beats per minute and regular, his respirations 18 per minute, and his oxygen saturation 78% (normal at 4200 m is 88%). His neurologic examination was otherwise unremarkable, including round, equal, and reactive pupils. After several minutes, the patient regained consciousness but was markedly confused and agitated. He was given 8 mg of dexamethasone via intramuscular injection and placed in a portable hyperbaric bag at 104 mmHg over ambient pressure. After 20 minutes, the patient was confused but no longer agitated. After 2 hours, the patient was alert and oriented, although he complained of occipital headache and nausea. He said that it was not the worst headache of his life. After hyperbaric treatment was discontinued, further examination yielded nonfocal neurologic results, including a supple neck, with the exception of slight ataxia found on heel-to-toe walking. His pulse was 100 beats per minute and regular, his blood pressure 155/85 mmHg, his respirations 16 per minute, his oxygen saturation 85%, and his oral temperature 98.5°F. An additional hour of hyperbaric treatment was administered while awaiting helicopter evacuation to Kathmandu. The suspected diagnosis was SAH, possibly with concurrent HACE. Lumbar puncture was not performed because of potential complications associated with this procedure in the setting of cerebral edema and because findings would not have directed a change in management during evacuation from the mountains.

On arrival in Kathmandu, the patient underwent physical and neurologic examination by a second physician and was found to be in normal condition. He did complain of neck pain, however, which was attributed to spondylosis of his cervical vertebrae based on radiographic findings. Because of the patient's history of headache and sudden loss of consciousness, a magnetic resonance imaging (MRI scan) of the head was obtained the following day to rule out a space-occupying lesion; findings were unremarkable. This physician suspected HACE that had resolved with descent to Kathmandu. As a precautionary measure, prompt return to Sweden for cerebral vascular imaging was recommended. Six days after the initial episode, while still in Kathmandu, the patient suddenly became confused, agitated, and ataxic. Lumbar puncture revealed bloody fluid under high pressure (not quantified) with a xanthochromic supernatant. An electrocardiogram and chest x-ray film were normal. The patient was medically evacuated to Sweden, where a cerebral angiogram revealed bleeding from a left middle cerebral artery aneurysm.

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ABBREVIATIONS USED IN TEXT

AMS = acute mountain sickness
HACE = high-altitude cerebral edema
MRI = magnetic resonance imaging
SAH = subarachnoid hemorrhage

Discussion

Global neurologic deterioration leading to unconsciousness is a prominent feature of both HACE and SAH. In cases of AMS sustained by unacclimatized individuals ascending to high altitudes, MRI routinely demonstrates increased intracranial pressure caused by diffuse brain swelling; this finding is associated with decreased extracerebral cerebrospinal fluid and ventricular volume resulting from hypoxia.[8] Subarachnoid hemorrhage results in blood escaping into the subarachnoid space surrounding the brain, causing meningeal irritation and an increase in intracranial pressure. Spontaneous SAH usually results from rupture of a congenital intracranial aneurysm. Less commonly, it may occur as the result of a mycotic or arteriosclerotic aneurysm, arteriovenous malformation, hemorrhagic disease, or head trauma.[9] Because the blood from an SAH surrounds the brain rather than flowing from within it,[10] global impairment of consciousness rather than focal neurologic deficit is characteristic of the syndrome, as with HACE.

In the case presented here, several clinical features differentiated high-altitude SAH from HACE. First, there was a notable absence of progressive mild symptoms of AMS with ascent; instead, the patient suddenly became symptomatic during descent. Second, sudden loss of consciousness without a gradual progression of neurologic symptoms is uncharacteristic of HACE. Third, the patient regained consciousness, although he was markedly confused and combative, before he received hyperbaric therapy. Finally, the persistent occipital headache following actual descent was alarming; HACE is known to clear rapidly with descent. These clinical features are consistent with the warning leaks frequently seen in patients with SAH prior to a disabling or fatal episode.[11]

Several factors may contribute to the risk of SAH at high altitude. The incidence of spontaneous SAH may increase with decreased barometric pressure.[12] The increase in cerebral blood flow that occurs at higher altitudes may make cerebral aneurysms and arteriovenous malformations more liable to bleed, perhaps in the same manner as retinal hemorrhages, which are very common at high altitude.[13] The response of blood pressure to acute altitude exposure is not clearly understood, but may also be involved in the onset of SAH.

MRI, which is less sensitive to subarachnoid blood than computerized tomography (CT) scanning,[10] yielded normal findings in this case. Results of spinal puncture, which is extremely sensitive to the presence of disseminated subarachnoid blood,[14] were positive after a subsequent bleeding episode in this patient while awaiting evacuation from Kathmandu to Sweden.

Conclusion

Any severe neurologic deterioration at high altitude calls for immediate and rapid descent to decrease cerebral edema and maximize oxygenation. However, recognition of acute intracranial bleeding or other neurologic emergency is also critical, because it may speed the evacuation from a remote area to a place where life-saving definitive care is available. Diagnosis of these neurologic conditions requires a careful history and examination early in the presentation, with attention to the possibility of neurologic illness other than AMS in the differential diagnosis of neurologic deterioration at high altitude. Any signs and symptoms of distress at high altitude that are notable for atypical onset, appear in unusual combinations, or persist after descent should alert health care providers to other possible emergencies in addition to high altitude illness.

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Editorial

Plaintiffs, Defendants, Lawyers, and Lawyers: Facts and Rumors About Silicone

As Marcia Angell explains so lucidly in her book *Science on Trial*,[1] the silicone gel breast implant story has exposed the conflict between scientific truth and the American system of justice.

Science is based on hypothesis, experimentation, sampling and statistical analysis, theories to explain new findings, all in a steady quest for understanding. The legal system, by contrast, seeks not truth but justice, based on the concept that the best way to achieve justice is in the adversarial arena of the courtroom.

In that arena, it is each lawyer's obligation to represent the case to the best of his or her ability. Viewed in this light, not only was it clever for Johnnie Cochran to play the race card so skillfully in the O.J. Simpson case—it was his duty. Not to have done so, in other words, would have deprived Simpson of the best defense he could have received. Final results notwithstanding, that's the American way.

Similarly, in the tens of thousands of lawsuits claiming injury from silicone gel breast implants, the plaintiff lawyers have only one goal: to convince the jury that their client, "that woman sitting across from you, ladies and gentlemen," has an illness that was likely induced by her breast implant. These lawyers have been extraordinarily successful, with tens of millions of dollars already paid in settlements and awarded at trials. A large, profitable company, Dow Corning, is in bankruptcy despite the fact that silicone accounted for about 1% of its revenues. And a class action settlement of more than $4 billion collapsed because there were insufficient funds to cover the claims.

What does all of this have to do with the issues usually covered in this journal? In this month's WESTERN JOURNAL OF MEDICINE (page 149), the line of reasoning followed by Genovese[2] exposes the vulnerability of the medical profession when it encounters the justice system. Genovese asks whether the particular patient he is discussing could have an illness related to silicone gel. Then, after comparing her symptoms and signs to those of the cases reported in various series, he concludes—rightly, I believe—that she had adult Still's disease.

But what if her symptoms had been less dramatic? Of the 1 million women with breast implants, or any other cohort of a million women of similar ages, one would expect thousands to develop fibromyalgia, not to mention rheumatoid arthritis, Raynaud's phenomenon, lupus, nonspecific aches and pains, malingering, bursitis—the stuff of a rheumatology practice.

If she had had fibromyalgia, or mild lupus, or Sjogren's syndrome, she would easily have fit the pattern described by people such as Solomon[3] and others who have been seeing patients on referral from plaintiff lawyers and pronouncing that virtually all of them have a disease caused by silicone. As reviewed nicely by Genovese, there is no scientific evidence that silicone gel implants cause systemic disease in any woman; therefore, the patient's specific symptoms could not be due to silicone, regardless of their nature.

Presumably because I was president-elect of the American College of Rheumatology, I was selected as a member of the 1992 FDA Breast Implant Panel. I went to the hearings determined to keep an open mind, but with a bias that the implants were probably causing disease. I had been intrigued by environmental causes of rheumatic disease, such as drug-induced lupus,[4] and had read the early reports on silicone. I had recently seen a Japanese woman die of fulminant scleroderma 25 years after having her breasts injected with unknown materials, and on one occasion I had recommended that a young woman with early scleroderma have her implants removed.

With that background, and after reviewing thousands of pages of Dow Corning files, toxicity studies from the 1960s, and similar documents from other companies and the FDA, I went to the hearings. I expected to hear epidemiologically based reports, or at least some convincing pattern of symptoms and laboratory findings.

What I heard, and continue to hear, was a litany of symptoms, signs, and laboratory findings that resembles any rheumatologist's office practice—any rheumatologist, that is, whose primary source of referral is plaintiff attorneys. The only things linking these women were breast implants and litigation. There was no new disease, and there is no new disease today.

Those plaintiff attorneys, by the way, are a well-organized bunch. They went after Bendectin first, then silicone, now Norplant, and there will be more. You can count on that, at least as long as the US remains unique in having juries hear civil cases and in allowing our lawyers to be paid by contingency fees. A third of a big number is still a big number.

What could we have done, and what should we do in the future, to prevent similar fiascos? I offer a few suggestions:

*See also "Fever, Rash, and Arthritis in a Woman With Silicone Gel Breast Implants" by Mark C. Genovese, MD, on pages 149–158 and "Scleroderma and Silicone Breast Implants" by Donald Wharton, MD, MPH, and Otto Wong, ScD, on pages 159–165 of this issue of THE WESTERN JOURNAL OF MEDICINE.

Note: Dr Sergent has participated as an expert witness in silicone breast implant litigation.

1. We need to protect our medical societies and journals from being abused. Abstracts presented at poster sessions on Saturday will be introduced as evidence in a courtroom on Monday. Anecdotal reports of no scientific merit should not be presented in scientific meetings or published in peer-reviewed journals unless there is solid evidence that the association is valid.
2. Our professional organizations need to be outspoken in defense of science. While later American College of Rheumatology presidents, most notably Shaun Ruddy, MD, did denounce the pseudo-science of the anecdotal reports, I and others should have been more outspoken.
3. We should establish rules of evidence. The courts traditionally look to professional groups to do just that, and in matters such as these the professional societies should take the lead in describing the kinds of scientific evidence that are germane to the issue.
4. Finally, we should learn how the legal system works. It is ruthless. It involves huge amounts of money. And it is not necessarily seeking truth, but instead seeking its adversarial version of justice.

I have learned a great deal since the FDA panel. By asking the question, "Could this patient have a silicone-induced disorder?", we are playing right into the hands of those who would have us believe that solid epidemiology is worthless, and that the junk science of clinical anecdote and irrelevant immunology should be our standard.

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Correspondence

Pulmonary Edema Following a Licorice Binge

To the Editor: Licorice has been known to cause hypertension, sodium and water retention, and hypokalemia through the hypermineralocorticoid effect of glycorrhizic acid.[1] There have been reports of peripheral and facial edema connected with licorice ingestion.

Pulmonary edema, however, is very unusual in conjunction with licorice consumption, and we have been able to find only one report without other comorbid conditions.[2] We here describe a case of pulmonary edema in which the only precipitating event was excessive consumption of licorice over a brief time period. We also review the available medical literature dealing with this subject.

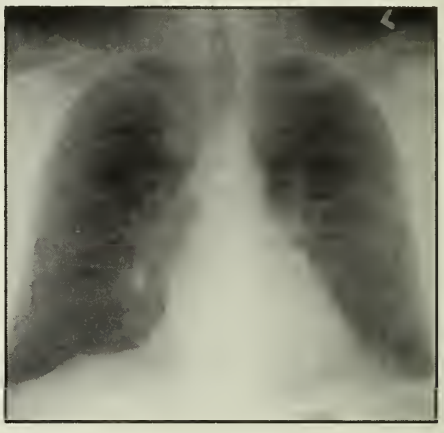

Figure 1.—Chest radiograph on admission with pulmonary edema.

Report of a Case

A 64-year-old previously healthy man came to the Salt Lake City VA Medical Center after 2 days of dyspnea on exertion, orthopnea, and fatigue. He described having eaten four packages (~1020 g) of black licorice (Hershey Twizzlers) during the previous 3 days. This amount of licorice contains ~3.6 g of glycorrhizic acid, a compound that ultimately can cause a pseudohypermineralocorticoid condition. The licorice binge was the patient's only deviation from his usual dietary or behavioral practices. On admission, his blood pressure was 180/80 mmHg. On physical examination, he appeared to be in mild respiratory distress with inspiratory crackles over the lower third of both lungs. Oxygen saturation was 90% on room air, potassium 3.5 mmol/l. A radiograph of the chest (Figure 1) showed cardiomegaly compared with prior films, bilateral pleural effusions, and bilateral interstitial edema. Serial electrocardiograms (ECGs), cardiac isoenzymes, and transthoracic echocardiogram were all normal. The patient was given 40 mg furosemide intravenously, several doses of oral enalapril, potassium, and oxygen, with complete resolution of pulmonary edema during the first 2 days in the hospital. A subsequent exercise thallium test did not reveal any pathology. The patient did not take any medications or eat any more licorice on discharge, and on follow-up 2 months later, was normotensive, without any shortness of breath, with a normal potassium level (4.5 mmol/l) and a normal chest radiograph (Figure 2). On outpatient clinic visits 8 and 13 months after discharge, the patient was still normotensive and without any signs of heart failure or hypokalemia.

Discussion

Only three cases of congestive heart failure after high doses of licorice have been reported previously.[2–4] The most recent case, and the only one without additional complicated issues, occurred after ingestion of 700 g of licorice candy over 9 days prior to the development of pulmonary edema.[2] In that report, however, the only measurements of heart function were an ECG, treadmill test, and chest radiograph. Edema has been reported previously with licorice, especially in the older medical literature; it has been used to treat Addison's disease.[3,4] In one report in which ulcers were treated by a licorice extract, "cardiac asthma" or edema was noted in 20% of patients.[5] Ours is the first case of pulmonary edema following licorice consumption in which significant structural heart abnormality has been ruled out. Despite the rarity of such occurrences, this consequence of a licorice binge warrants attention.

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Figure 2.—Chest radiograph 2 months after discharge.

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Food Poisoning in Flight

To the Editor: Inflight medical emergencies are rare but can be extremely serious, especially when they occur during extended international flights. In 1992, for example, 75 passengers on a commercial airline flight from Lima, Peru, to Los Angeles were diagnosed with cholera; 10 were hospitalized and one died.[1] These emergencies often present a management dilemma because of the limited onboard medical resources available, the length of time spent in the air, and the sparsity of nearby landing sites. Recently my wife and I, together with our 1-year-old daughter, were flying back to the US from a vacation in Pakistan when we encountered a challenging case of severe food poisoning.

One of our fellow passengers was a 62-year-old woman who was returning to the United States after 3 weeks of missionary work in India. She was healthy and had no significant medical history. Her stay in India had been uneventful. She had eaten her last meal in India just before boarding the airplane. She had a good appetite, and had two inflight meals before our plane arrived in Tokyo. After a short stopover in that city, the plane departed for Los Angeles. Two hours after the inflight dinner was served (roughly 15 hours after she boarded the flight from India), she began to develop severe vomiting and diarrhea accompanied by abdominal cramps so painful and intense that she could not even make it to the restroom. Her diarrhea was profuse, watery, and uncontrolled. She was pale, diaphoretic, and very weak, and the flight crew requested help from any onboard physicians. My wife and I (a practicing internist and a gastroenterolology fellow, respectively) volunteered to assist. We found the woman in a semiconscious state in her seat, soiled with feces. She appeared toxic, with sunken eyes and dry mucous membranes. She was awake but very lethargic. We were stunned at how sick and miserable she looked. We immediately placed her flat on the floor and requested the emergency medical kit. We were relieved for a brief moment when we noted that her supine blood pressure was 107/70 mmHg with a pulse of 80 beats per minute. Her abdomen was soft, with mild diffuse tenderness and hyperactive bowel sounds. The medical kit contained a liter of intravenous fluid, along with a few other medications. We inserted an intravenous line, rapidly administered fluids, and gave her 10 mg of prochlorperazine via intramuscular injection to control her persistent vomiting. Flight attendants helped us clean her, but despite all efforts the patient continued to soil herself. At this time Los Angeles was still 7 hours away. With no more intravenous fluids available and with the patient showing persistent signs of severe dehydration, possible electrolyte imbalance, and impending shock, the situation appeared critical. We discussed the seriousness of her condition with the pilot and flight crew, and we made the decision to land the plane at the nearest airport, Honolulu, Hawaii—still 2 hours away. During this time the patient remained comfortable, with no further episodes of vomiting but with continued diarrhea. Upon our arrival in Honolulu paramedics transported the patient to the nearest hospital and our flight resumed soon after refueling. None of the other passengers developed any symptoms of food poisoning, which suggested that our patient had most likely contracted the infection (possibly salmonella or shigella food poisoning) before boarding the plane in India.

For several hours during the flight my wife and I were stressed and challenged by the severity of the patient's condition and the lack of adequate medical supplies. Making an emergency landing in the interest of the patient was a major decision, since it delayed arrival in Los Angeles for more than 350 passengers, some of whom missed their onward connections. Our unscheduled stopover might well have been avoided if we had had the supplies necessary to alleviate the patient's condition on board.

This was a classic case of food poisoning, with its life-threatening complications of severe dehydration and shock.[2] Our patient could not be sufficiently hydrated; this placed her life in grave danger. Clearly, airlines need to consider improving their onboard emergency medical preparedness. This would mean ensuring adequate and appropriate supplies and perhaps even training crew members to handle inflight medical emergencies. We have written the Federal Aviation Administration (FAA) recommending that airliners carry more intravenous fluids, especially on long international flights.

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2. Parkin DM, Clayton D, Black RJ, Masuyer E, Friedl HP, Ivanov E, et al. Childhood leukaemia in Europe after Chernobyl: 5 year follow-up. Br J Cancer 1996; 73:1006–1012

No author given:

3. Cancer in South Africa [editorial]. S Afr Med J 1994; 84(12):15

Books

4. Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996 [author of book is same as author of chapter]

5. Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995, pp 465–478 [authors of book differ from chapter author]

Correspondence

6. Shusterman D. Espresso maker's wrist [correspondence]. West J Med 1990; 152:721–722

Scientific or Technical Report

Issued by funding or sponsoring agency:

7. Smith P, Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX): Dept of Health and Human Services (US), Office of Evaluation and Inspections; 1994 Oct. Report No.: HHSIGOEI69200860

Issued by performing agency:

8. Field MJ, Tranquada RE, Feasley JC, editors. Health services research: work force and educational issues. Washington DC: National Academy Press; 1995. Contract No.: AHCPR282942008. Sponsored by the Agency for Health Care Policy and Research

9. Centers for Disease Control and Prevention. Recommendations and Reports: 1997 Revised guidelines for performing CD4+ T-cell determinations in persons infected with human immunodeficiency virus (HIV) MMWR 1997; 46(Jan 10):RR-2

Proceedings

10. Kimura J, Shibasaki H, editors. Recent advances in clinical neurophysiology. Proceedings of the 10th International Congress of EMG and Clinical Neurophysiology; 1995 Oct 15–19; Kyoto, Japan. Amsterdam: Elsevier; 1996

Mass Circulation Publications

11. Lee G. Hospitalizations tied to ozone pollution: study estimates 50,000 admissions annually. The Washington Post 1996 Jun 21; Sect A:3 (col 5)

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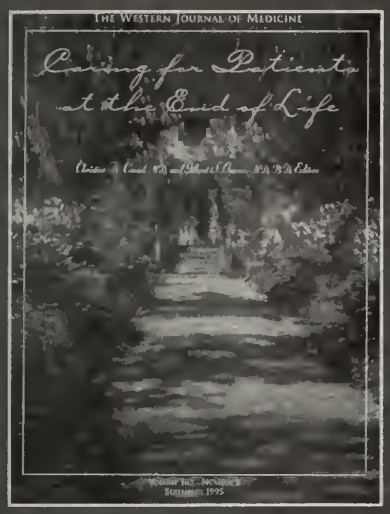

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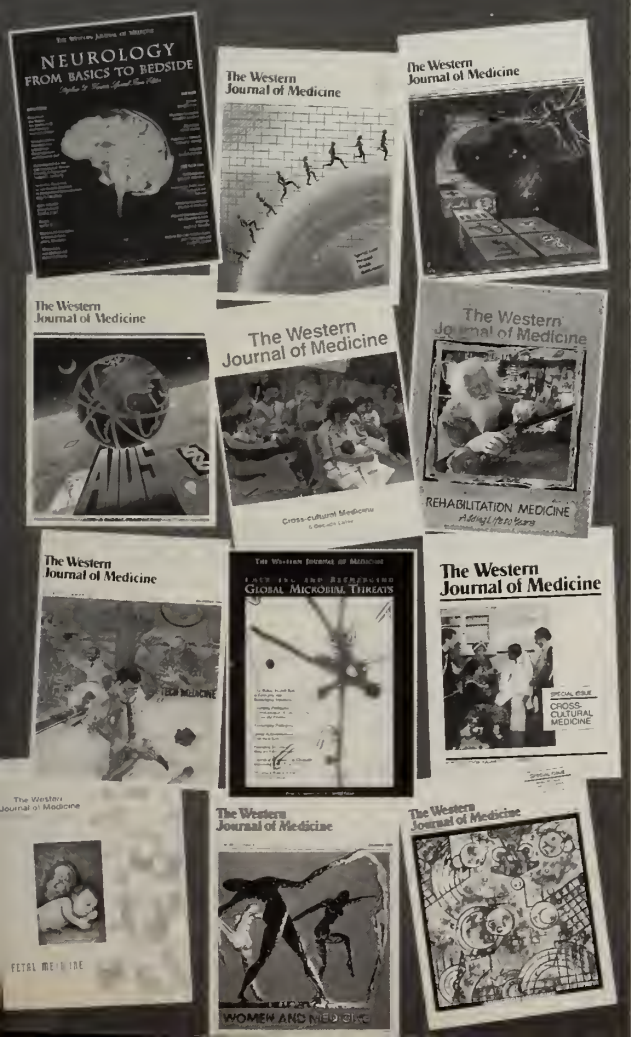

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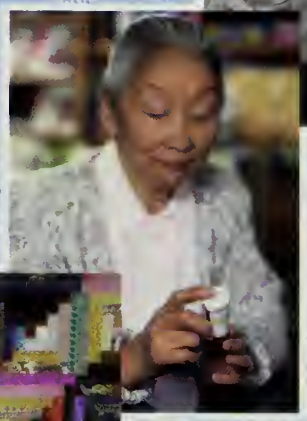

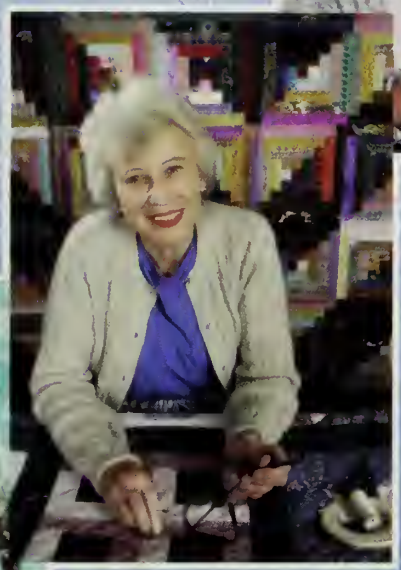

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VOLUME 167 • NUMBER 4 • OCTOBER 1997

CONTENTS

Successful Aging

ERIC B. LARSON, MD, MPH, Guest Editor

203 **Successful Aging: Now Is The Time**

LINDA HAWES CLEVER, MD

204 **Successful Aging: An Overview**

ERIC B. LARSON, MD

Dr Larson is Medical Director and Professor of Medicine, University of Washington Medical Center, Seattle

206 **Ways to Make "Usual" and "Successful" Aging Synonymous—Preventive Gerontology**

WILLIAM R. HAZZARD, MD

From the Department of Internal Medicine and the J. Paul Sticht Center on Aging, Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina.

216 **Building Communities That Promote Successful Aging**

LINDA P. FRIED, MD, MPH; MARC FREEDMAN, MS; THOMAS E. ENDRES; and BARBARA WASIK, PhD

From the Welch Center for Prevention, Epidemiology and Clinical Research and the Center for Social Organization of Schools, Johns Hopkins University, Baltimore, Md (Drs Fried and Wasik); Public/Private Ventures, Berkeley, Ca (Mr Freedman); and the Corporation for National Service, Washington, DC (Mr Endres).

220 **Healthy Aging—A Women's Issue**

ANDREA Z. LA CROIX, PhD; KATHERINE M. NEWTON, PhD; SUZANNE G. LEVEILLE, PhD; and JEFFREY WALLACE, MD, MPH

From the Fred Hutchinson Cancer Research Center, Public Health Sciences Division (Dr LaCroix), and the Center for Health Studies, Group Health Cooperative of Puget Sound, Seattle, Washington (Drs LaCroix and Newton); the Epidemiology, Demography and Biometry Program, National Institute on Aging, National Institutes of Health, Bethesda, Maryland (Dr Leveille); and the Division of Geriatrics, Department of Medicine, University of Washington School of Medicine, Seattle, Washington (Dr Wallace).

233 **Optimal Medication Use in Elders—Key to Successful Aging**

MARK MONANE, MD, MS; SUSAN MONANE, RN, MSN; and TODD SEMLA, PharmD

From the Medical Policy and Programs Division, Department of Medical Affairs, Merck-Medco Managed Care, LLC, Montvale, New Jersey (Dr and Ms Monane); and the Department of Pharmacy, St Francis Hospital, Evanston, Illinois (Dr Semla).

238 **Successful Aging Calls for More than Drugs**

WILLIAM B. ERSHLER, MD, and STEFAN GRAVENSTEIN, MD

From the Gerontology Research Center, National Institute on Aging, Baltimore, Maryland, and the Glennan Center for Geriatrics and Gerontology, Eastern Virginia Medical School, Norfolk, Virginia.

240 **Heart Health in Older Adults—Import of Heart Disease & Opportunities for Maintaining Cardiac Health**

LINDA P. FRIED, MD, MPH; ROBERT L. MCNAMARA, MD, MHS; GREGORY L. BURKE, MD, MS; and DAVID S. SISCOVICK, MD, MPH

From the Johns Hopkins University School of Medicine, Baltimore, Md (Drs Fried and McNamara); Bowman Gray School of Medicine at Wake Forest University/Baptist Hospital and Medical Center, Winston-Salem, NC (Dr Burke); and the University of Washington School of Medicine, Seattle (Dr Siscovick).

247 **Hear Ye? Hear Ye! Successful Auditory Aging**

GEORGE A. GATES, MD, and THOMAS S. REES, PhD

From the Department of Otolaryngology–Head and Neck Surgery, University of Washington School of Medicine, Seattle.

253 **Seeing Into the Future—Vision and Aging**

ROBERT E. KALINA, MD

From the Department of Ophthalmology, University of Washington School of Medicine, Seattle.

258 **Preserving Mobility in Older Adults**

DAVID M. BUCHNER, MD, MPH

From the Department of Health Services and the Northwest Prevention Effectiveness Center, University of Washington School of Medicine, and the Northwest Center for Outcomes Research in Older Adults, Veterans Affairs Puget Sound Health Care System, Seattle, Washington

265 **Overcoming Barriers to Successful Aging—Self-Management of Osteoarthritis**

HALSTED R. HOLMAN, MD, and KATE R. LORIG, DrPH

From the Division of Immunology and Rheumatology, Stanford University School of Medicine, Palo Alto, California

269 **Memory, Thinking, and Aging—What We Know About What We Know**

LINDA TERI, PhD; SUSAN M. MCCURRY, PhD; and REBECCA G. LOGSDON, PhD

From the Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle.

276 **Maintaining Good Morale in Old Age**

MARK D. SULLIVAN, MD, PhD

From the Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle.

285 **Aging and Sexuality**

CINDY M. MESTON, PhD

From the Reproductive and Sexual Medicine Clinic, University of Washington School of Medicine, Seattle.

291 **Community Resources for Frail Older Patients**

KATHRYN BORGENICHT, MD; ELIZABETH CARTY, MSW; and LAWRENCE Z. FEIGENBAUM, MD

From the Department of Medicine, University of California, San Francisco (Drs Borgenicht and Feigenbaum), OnLok Senior Health Center (Dr Borgenicht), and the Goldman Institute on Aging (Dr Borgenicht, Ms Carty, and Dr Feigenbaum), San Francisco.

295 **Preventing Decline in Function—Evidence from Randomized Trials Around the World**

EDWARD H. WAGNER, MD, MPH

From the Center for Health Studies, Group Health Cooperative of Puget Sound; Northwest Prevention Effectiveness Center; University of Washington School of Public Health and Community Medicine, Seattle.

OTHER FEATURES

194 WJM Subscription Information

197 Continuing Medical Education Activities

299 Classified Advertising

302 Instructions for Authors

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (520) 626-7832; (800) 328-5868.

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ALLERGY

January 18–23, 1998—**36th Annual Scientific Session of The Western Society of Allergy and Immunology.** Four Seasons Resort, Wailea in Maui, Hawaii. For more information contact Rebecca Gough, Exec. Administrator, PO Box 1122, Roanoke, Texas, 76262; (817) 491-2616, Fax (817) 491-2241.

ANESTHESIOLOGY

November 14–16—**9th Annual Anesthesiology Update, 1997.** UC Davis at Monterey Plaza Hotel. Fri.–Sun. Contact: (916) 734-5390.

January 7–10, 1998—**UCSD Anesthesiology Update 1998.** UCSD at Hotel del Coronado, San Diego. Wed.–Sat. 18 hrs. Contact: Carol Heil (619) 543-2188.

CARDIOLOGY

November 1, 1997—**Cardiology.** Ritz-Carlton Huntington Hotel, Pasadena. Sat. 5.5 hrs. Cost: $40.00. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

December 12–14—**15th Annual Advances in Heart Disease.** American College of Cardiology at Grand Hyatt on Union Square San Francisco. Fri.–Sun. 16 hrs. Contact: ACC Registration Secretary, Extramural Programs Dept., (800) 253-4636, ext. 695.

January 16–17, 1998—**Radiotherapy to Reduce Restenosis.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri.–Sat. 16.5 hrs. Contact: Laurel Steigerwald, Scripps Clinic Dept. Academic Affairs 403c, 10666 N. Torrey Pines Road, La Jolla, 92037 (619) 554-8556.

January 24, 1998—**Heart Failure.** Ritz-Carlton Huntington Hotel, Pasadena. Sat. 5 hrs. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

January 30–February 1, 1998—**Clinical Nuclear Cardiology: Case Review With the Experts.** American College of Cardiology at Cedars-Sinai Medical Center, Los Angeles. Fri.–Sun. 19 hrs. Contact: ACC Registration Secretary, Extramural Programs Dept., (800) 253-4636, ext. 695.

February 19–21, 1998—**Cardiovascular Health: Coming Together for the 21st Century.** UCSF at Hyatt Regency Embarcadero San Francisco. Thurs.–Sat. Contact: UCSF.

COMPUTER TECHNOLOGY

November 20–22—**Computer Training for Physicians.** UCSD at National University San Diego. Thurs.–Sat. 18 hrs. $575. Contact: OCME (619) 534-3940.

December 11–13—**Computer Training for Physicians.** UCSD at National University San Diego. Thurs.–Sat. 18 hrs. $575. Contact: OCME (619) 534-3940.

January 28–31, 1998—**Medicine Meets Virtual Reality: Art, Science, Healthcare Evolution.** UCSD at San Diego Hyatt Regency. Wed.–Sat. Contact: Karen Morgan (760) 751-8841.

DERMATOLOGY

January 15–18, 1998—**Practical Dermatology for the Primary Care Physician.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency La Jolla, San Diego. Method, AV, L, SB, W. $575. Thurs.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

January 31–February 1—**Melanoma 1998: 8th Annual Cutaneous Malignancy Update.** Scripps Clinic at Scripps Memorial Hospital, La Jolla. Sat.–Sun. 11.5 hrs. Contact: Jill Hofmans, Scripps Clinic, (619) 554-8556.

May 3–6, 1998—**Practical Dermatology for the Primary Care Physician.** Las Vegas. Sponsored by Continuing Medical Education Associates. Caesar's Palace Las Vegas. Method, AV, L, SB, W. $575. Sun.–Wed. 20 hrs. credit: AMA, AOA, AAP, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

EMERGENCY MEDICINE

October 27–31—**26th Annual Topics in Emergency Medicine.** UCSF at Radisson Miyako Hotel San Francisco. $725. Mon.–Fri. 32 hrs. Contact: UCSF.

November 10–14—**Emergency Medicine Symposium II.** UCSD at La Jolla Marriott. Mon.–Fri. 32 hrs. $495. Contact: OCME (619) 534-3940.

December 15–19—**Emergency Medicine Symposium II.** UCSD at UCSD San Diego. Mon.–Fri. 32 hrs. $495. Contact: OCME (619) 534-3940.

February 27–March 3, 1998—**Critical Care Medicine.** Las Vegas Hilton Hotel, Las Vegas. Fri.–Tues. 26 hrs. Cost: $785/MD, $585/Allied Health. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

February 16–20, 1998—**Emergency Medicine Symposium I.** UCSD at La Jolla Marriott San Diego. $495. Mon.–Fri. 32 hrs. Contact: OCME (619) 534-3940.

May 15–16, 1998—**Trauma/Critical Care.** Ritz-Carlton Huntington Hotel, Pasadena. Mon.–Tues. 14 hrs. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

FAMILY PRACTICE/PRIMARY CARE

October 25—**Management of Type 2 Diabetes.** Sheraton Grande Hotel, Los Angeles. Sun. 5.5 hrs. $35. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

November 20–22—**Women's Health Issues in Primary Care.** UCSD at Hyatt Regency, La Jolla. Thurs.–Sat. 18 hrs. $300. Contact: OCME (619) 534-3940.

December 6—**Management of Type 2 Diabetes.** Sheraton Grande Hotel, Los Angeles. Sun. 5.5 hrs. $35. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

May 15–19, 1998—**Primary Care Essentials.** San Francisco. Sponsored by Continuing Medical Education Associates. Grand Hyatt on Union Square San Francisco. Method, AV, L, SB, W. $750. Fri.–Tues. 32 hrs. credit: AMA, AOA, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

GERIATRICS

November 10–12—**Geriatrics Update, 1997.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $475. Mon.–Wed. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

INFECTIOUS DISEASE

November 7–9—**Advances in Infectious Disease.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $475. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

February 6–7, 1998—**16th Annual Infectious Disease Conference.** UC Davis Medical Center at Sacramento Hilton Inn. Fri.–Sat. Contact: (917) 734-5390.

INTERNAL MEDICINE

November 22—**Management of Dyspepsia, Peptic Ulcer Disease and Gastric Cancer.** Sat. 4 hrs. $20. Contact: OCME (619) 534-3940.

March 7–14, 1998—**Diagnostic & Therapeutic Skills in Internal Medicine.** Mauna Kea Beach Hotel, Kameula, HI. Mon.–Fri. 27 hrs. $635. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

March 20–26, 1998—**Internal Medicine 1998.** San Diego. Sponsored by Continuing Medical Education Associates. Hotel del Coronado San Diego. Method, AV, L, SB, W. $795. Fri.–Thurs. 45 hrs. credit: AMA, AOA, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

NEPHROLOGY

January 29–31, 1998—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at La Jolla Marriott. Thurs.–Sat. 17 hrs. $425.

NEUROLOGY

October 25—**"Brain Attack!" '97.** UCLA Stroke Center at Beverly Hilton, Beverly Hills. Sat. 6.5 hrs. Contact: Office of CME (310) 794-2620.

December 6—**Movement Disorders.** Hotel Sofitel, Los Angeles. Sat. 5.25 hrs. $25. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

January 31, 1998—**UCLA Neurology: Update for Primary Care Physicians.** Miramar Sheraton Hotel Santa Monica. 6 hrs. Contact: Sheryl Crowley, Office of Continuing Medical Education, 10920 Wilshire Blvd., Los Angeles 90024-6512 (310) 794-2620; Fax (310) 794-2624..

February 11–13, 1998— **Recent Advances in Neurology.** UCSF at Fairmont Hotel San Francisco. Wed.–Fri. 15 hrs. Contact: UCSF (415) 476-4251.

March 20, 1998—**STROKE: Van Der Meulen Symposium in Clinical Science.** USC Health Sciences Campus, Los Angeles. Fri. 7 hrs. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

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November 1–5—**1996–1997 Temporal Bone Surgical Dissection Courses.** The House Ear Institute at Los Angeles. Sat.-Wed. 48 hrs. $1,300. Contact: House Ear Institute, 2100 W. Third St., Los Angeles 90057. (213) 483-4431, ext. 7079.

January 16–18, 1998—**California Association of Neurological Surgeons Annual Session.** Parc Fifty Five Hotel, San Francisco. 7 hrs. Contact: Janine Tash, 5380 Elvas Ave., Ste. 216, Sacramento 95819, (916) 457-2267, fax (916) 457-8202.

OB/GYN

February 14–20, 1998—**Perinatal Medicine.** Westin Maui Hotel, Maui, HI. Mon.–Thur. 20 hrs. $625. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

February 12–15, 1998—**Office Gynecology and Women's Health for the Primary Care Physician.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Islandia San Diego. Method, AV, L, SB, W. $575. Thurs.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 28–March 3, 1998—**15th Annual OB/GYN Update: 1998.** UC Davis Medical Center at South Lake Tahoe. Sat.–Tues. Contact: (917) 734-5390.

ONCOLOGY

October 25—**Interventional Approach to Cancer Care.** St. Mary Medical Center at Holiday Inn Victorville. Sat. 8 hrs. $90. Contact: Yvonne Newton, CTR, St. Mary Regional Medical Center, 18300 Highway 18, Apple Valley, 92307 (760) 242-2311, ext. 6111.

November 8—**Treatment & Management of Cancer.** Ritz-Carlton Huntington Hotel, Pasadena. Sat. 5.5 hrs. $25. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

December 7—**103rd Semi-Annual Seminar: Cutaneous Neoplasms.** California Tumor Tissue Registry at Sheraton Palace Hotel San Francisco. $265. Sun. 8 hrs. Contact: Loma Linda University (909) 824-4788.

January 16–17, 1998—**Radiotherapy to Reduce Restenosis.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri.–Sat. 16.5 hrs. Contact: Laurel Steigerwald, Scripps Clinic Dept. Academic Affairs 403c, 10666 N. Torrey Pines Road, La Jolla, 92037 (619) 554-8556.

February 16–19, 1998—**Clinical Hematology & Oncology.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel La Jolla. Fri.–Mon. 24 hrs. Contact: Laurie A. Regis, Scripps Clinic (619) 554-8556.

ORTHOPEDICS

April 23–26, 1998—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency San Francisco. Method, AV, L, SB, W. $575. Thurs.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

May 3–6, 1998—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Las Vegas. Sponsored by Continuing Medical Education Associates. Caesar's Palace Las Vegas. Method. AV, L, SB, W. $575. Sun.–Wed. 20 hrs. credit: AMA, AOA, AAP, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Education Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education, (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

OTOLARYNGOLOGY

November 1–5—**1996-1997 Temporal Bone Surgical Dissection Course.** House Ear Institute at Los Angeles. Sat.–Wed. 48 hrs. $1300. Contact: House Ear Institute, 2100 W. Third St., Los Angeles, CA 90057. (213) 483-4431, ext. 7079.

PEDIATRICS

October 25–28—**Pediatric Facial Plastic Surgery.** UCD at Monterey Plaza Hotel. Sat.–Tues. Contact: UCD.

December 6–7—**Stabilization and Management of Critically Ill Child.** UCSF at Embarcadero Hyatt Regency Hotel San Francisco. Sat.–Sun. Contact: UCSF (415) 475-4251.

January 24, 1998—**Update in Behavioral/Developmental Pediatrics.** UCSF at campus of UCSF. Sat. Contact: UCSF.

February 6–11, 1998—**PREP the Course.** AAP at Fairmont Hotel San Francisco. Fri.–Wed. 44 hrs. Contact: AAP (800) 433-9016, ext. 6796 or 7657.

February 15–18, 1998—**Pediatrics Update 1998.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Islandia San Diego. Method, AV, L, SB, W. $575. Sun.–Wed. 20 hrs. credit: AMA, AOA, AAP, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 16–19, 1998—**Clinical Hematology and Oncology: 1998.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel La Jolla. Fri.–Mon. 24 hrs. Contact: Laurie A. Regis, Scripps Clinic (619) 554-8556.

PSYCHIATRY

November 14–16—**43rd Annual Group Therapy Symposium.** UCSF at Mark Hopkins Hotel. San Francisco. Fri.–Sun. 20 hrs. $340. Contact: UCSF.

RADIOLOGY

January 16–17, 1998—**Radiotherapy to Reduce Restenosis.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri.–Sat. 16.5 hrs. Contact: Laurel Steigerwald, Scripps Clinic Dept. Academic Affairs 403c, 10666 N. Torrey Pines Road, La Jolla, 92037 (619) 554-8556.

SURGERY

December 12–13—**Annual Advanced Seminar in Urologic Surgery.** UCSF at Ritz-Carlton Hotel San Francisco. Fri.–Sat. 14.5 hrs. Contact: UCSF (415) 476-4251.

April 16–18, 1998—**Techniques in Arthritis Surgery.** Ritz-Carlton Huntington Hotel, Pasadena. Wed.–Sat. 24 hrs. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

May 9, 1998—**Thyroid Update '98.** Sheraton Grande Hotel, Los Angeles. Sat. 7 hrs. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

GENERAL/MULTIDISCIPLINARY

October 25–26—**ACLS Provider.** AHA at San Francisco. Fri. 16 hrs. $170. Contact: CPR Seminars (510) 632-6135.

October 31–November 3—**Spanish for the Medical Profession.** San Diego. Maricopa Health System. $695. 36 hrs. Contact: Joanna Rios, 1351 E. Ft. Lowell Road, Suite C, Tucson, AZ 85719. (619) 218-4875 or (520) 881-3295.

November 3–6—**Orientation Course in Hyperbaric Medicine.** Long Beach Memorial Medical Center. Mon.–Thurs. 27.5 hrs. $550. Contact: Celia Loney or Don Winant (562) 933-6951.

November 7—**Wound Care Symposium.** Long Beach Memorial Medical Center. Fri. 7.5 hrs. $100. Contact: Celia Loney or Don Winant (562) 933-6951.

November 22—**Disease Drugs and Dollars: Diabetes, AIDS, Medi-Cal Transition, Managed Care.** USC Health Sciences Campus, Los Angeles. Sat. 3 hrs. $25. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

December 5–8—**Spanish for the Medical Profession.** Los Angeles. Maricopa Health System. $695. 36 hrs. Contact: Joanna Rios, 1351 E. Ft. Lowell Road, Suite C, Tucson, AZ 85719. (619) 218-4875 or (520) 881-3295.

January 28–31, 1998—**Medicine Meets Virtual Reality: Art, Science, Technology: Healthcare (R)Evolution.** San Diego Hyatt Regency. Wed.–Sat. Contact: AMA, Inc. (760) 741-8841.

January 31–February 2, 1998—**Spanish for the Medical Profession.** San Diego. Maricopa Health System. $695. 36 hrs. Contact: Joanna Rios, 1351 E. Ft. Lowell Road, Suite C, Tucson, AZ 85719. (619) 218-4875 or (520) 881-3295.

February 13–16, 1998—**California Academy of Family Physicians 50th Annual Scientific Assembly.** Anaheim Hilton and Towers. $275–$385. 26+ hrs. Contact: Clark W. Franklin, California Academy of Family Physicians, 114 Sansome St., Suite 1305, San Francisco, CA 94104-3824. (415) 394-9121; fax (415) 394-9119; Email: cfranklin@familydocs.org.

February 25–March 1, 1998—**7th Annual Winter Board Review for Physician Assistants.** Holiday Inn, Pasadena. Wed.–Sun. 30 hrs. $345; $245 student rate. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

HOME STUDY/SELF-ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

The listing of continuing medical education programs in Idaho is compiled by the Ada County Medical Society. To list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701. (208) 336-2930.

Brochures, course information, and registration forms are available from the contact person or organization.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information

on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

January 23–24, 1998—**28th Annual Winter Pediatric Orthopaedic Seminar.** Albuquerque. Fri.-Wed. Contact: UNM Continuing Medical Education, Campus Box 713, Albuquerque, NM 87131-5126. (505) 272-3942, fax (505) 272-8604.

January 24–25, 1998—**16th Annual Albuquerque Family Practice Seminar.** Radisson Hotel Carlisle at I-40, Albuquerque. Sponsor: New Mexico Academy of Family Physicians. Contact: Ann Woodrow, (505) 243-4560..

February 25–28, 1998—**Advances in Neurology.** Santa Fe. Contact: UNM Continuing Medical Education, Health Sciences and Services Building, Room 140, Box 713, Albuquerque, NM 87131-5126. (505) 272-3942, fax (505) 272-8604 or e-mail dmurray@unm.edu..

March 20–21, 1998—**Advances in Primary Care.** Albuquerque. Crowne Plaza Hotel. Contact: UNM Continuing Medical Education, Campus Box 713, Albuquerque, NM 87131-5126. (505) 272-3942, fax (505) 272-8604.

Satellite Courses

Immunization Update 1997
September 17

Hepatitis C
Sometime in November

Contact: Joe Treat or Jim Cato, Immunization Program, (505) 827-2366

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.

DM: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.

ETS: Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.

FHP: FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UANS: Utah Association of Neurological Surgeons, 24 S 1100 East, Ste 302, Salt Lake City 84102. (801) 531-7806.

UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

OTHER CME OPPORTUNITIES

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. November 14–16—**Scottsdale Headache Symposium**. Scottsdale at Marriott's Camelback Inn Resort & Spa. Contact: (609) 845-1720.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. January 16–18, 1998—**Headache Now/Cancun**. The Ritz-Carlton, Cancun, Mexico. Contact: (609) 845-1720

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. June 26–28, 1998—**Fortieth Annual Scientific Meeting of The American**

Association for the Study of Headache. Sheraton Palace, San Francisco. Contact: (609) 845-1720

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. November 6–8, 1998—**Scottsdale Headache Symposium**. Scottsdale at Marriott's Camelback Inn Resort & Spa. Contact: (609) 845-1720..

AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE. October 26–30—**49th Annual State-of-the-Art Conference**. Opryland Hotel, Nashville, Tennessee. Sun.–Thur. Contact: ACOEM, 55 W. Seegers Rd., Arlington Heights, Ill 60005. (847) 228-6850, ext. 184, FAX (847) 228-1856; Website: www.acoem.org.

AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE. April 24–May 1, 1998—**57th American Occupational Health Conference**. Boston, Mass. Contact: ACOEM, 55 W. Seegers Rd., Arlington Heights, Ill 60005. (847) 228-6850, ext. 184, FAX (847) 228-1856; Website: www.acoem.org.

Arrhythmias: Interpretation, Diagnosis & Management. *October 31–November 1*, Le Meridien, San Diego. *December 12–14*, Monte Carlo Hotel, Las Vegas, NV. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

The Atopy Syndrome in the Third Millenium. *October 2–3, 1998*, Zurich, Switzerland, on the occasion of the 50th anniversary of the allergy unit at the Dept of Dermatology, University Hospital, Zurich, and in collaboration with the European Academy of Allergology and Clinical Immunology. Contact: Prof. Dr. B. Wüthrich, Zurich, 41-1-255-3079, fax 41-1-255-4431.

Coronary Heart Disease Update. *November 21–23*, Monte Carlo Hotel, Las Vegas, NV. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731

Dermatology for the Non-Dermatologist. *November 21–23*, Disneyland Pacific Hotel, Anaheim, CA. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

Managing Respiratory Diseases. *October 31–November 2*, The Phoenician Resort, Scottsdale, AZ. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

UNIVERSITY OF NEBRASKA. December 11–13—**Obstetrics & Gynecology Conference**. Bally's, Las Vegas, NV. Thu.-Sat. $325. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha NE 68198-5651. (800) 642-1095.

NOTICE

State Associations should send their CME listings for publication to:

Allison Spearman, Managing Editor
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A Special Issue of

The Western Journal of Medicine

SUCCESSFUL AGING

Eric B. Larson, MD, MPH, Guest Editor

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WILLIAM R. HAZZARD, MD

Building Communities That Promote Successful Aging
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Now Is The Time

Ponce de León's search for the Fountain of Youth came to naught but many have taken up his quest. A more practical approach is highlighted in this special issue of THE WESTERN JOURNAL OF MEDICINE, "Successful Aging." This effort is part of a shared vision by nearly 100 medical journals from 33 countries to focus on aging during the month of October, 1997. We started in September 1996, when 108 editors from around the world narrowed 97 proposed topics of special interest and importance to 12 and then to 1. The 12 included environment and health, cancer, genetics and molecular medicine, cost effectiveness analysis, and women's health. Aging ranked at the top of every list. Its position reflected demographics, public demands, research priorities, and, possibly, personal concerns (editors tend to have a certain patina).

This issue represents months of envisioning, discussing, planning, recruiting, writing, reviewing, and editing. Eric Larson, MD, MPH, Professor of Medicine at the University of Washington, is the Special Editor with splendid help from Edward H. Wagner, MD, MPH, Professor of Health Services & Community Medicine at the University of Washington School of Public Health, Seattle. In addition to his responsibilities as the Medical Director of the University of Washington Medical Center, Dr. Larson is internationally known as a brilliant practitioner and teacher of general internal medicine with special interests in aging and, in particular, dementia. We are deeply grateful that Drs. Larson and Wagner have assembled a top notch group of authors to present current research and thinking on maintaining and enhancing the function of the heart, mind, ears, eyes, muscles, bones and joints, and even the spirit. We learn that successful aging is more than a matter of good genes, good habits, and good luck. It requires that individuals make good choices to avoid bad consequences. It also often requires building and using community resources as well as education, medications, special measures to prevent disease and complications, and wise counseling of patients and families by physicians and others.

Ponce de León was battered during his trek. We doubtless could give him high points for exercise and possibly nutrition, but he was dogged by pesky bugs, venomous snakes, sharp-toothed reptiles, sucking swamps, and interpersonal conflicts. Perhaps his life's realities are our lives' metaphors. We may not face his extremes, but we do face challenges.

The goal of this issue is to help practitioners stave off or moderate the battering afforded to bodies and souls by time and circumstances. Experienced clinicians know the importance of competent care, good advice, and good companionship throughout life, especially in older years. This issue will enable physicians and others to base their comprehensive care on new, tested knowledge. The sooner it is applied, the better.

LINDA HAWES CLEVER, MD

Successful Aging

An Overview

ERIC B. LARSON, MD, MPH, *Seattle, Washington*

(Larson EB. Successful aging: an overview. In: Successful Aging. West J Med 1997; 167:204–205)

For a long time, developmental research in biology, medicine, and the social sciences was mostly directed to infancy and adolescence. With the aging of society, interest began to grow in the study of late adult life, a stage of life that is as forceful and full of changes and transitions as life before 20. We now know considerably more about aging than we did in the 1970s, when geriatrics became a recognized discipline and specialty in medicine.

Most of what we have learned about aging relates to so-called physiologic decline and the diseases of aging—that is, normal and abnormal aging. This knowledge of geriatrics has helped our patients. At the same time, many of our patients are asking for more. Frequently they ask their physicians, "What are the possibilities that I can *live*, not suffer, as I age?" Patients tell us: "It's sure no fun getting old." I used to respond by smugly saying: "It sure beats the alternative of not getting older—dying!"

Now I believe we need to be more sympathetic to our patients' message that it is "no fun getting old" and provide them with advice, skills, and treatments that help minimize age-related decline. Patients also want to reduce the risk of having age-related disease or to minimize the disability of these chronic diseases.

The growing number of old-old persons, and the basic human drive to stay well, accounts for the strong interest in successful aging.

This special issue of The Western Journal of Medicine is devoted to exploring various aspects of successful aging.

One of the chapters in a book entitled *Successful Aging* begins with the statement, "There is no consensus as to what the term successful aging means."[1] The volume includes contributions from social, biological, and medical scientists who describe successful aging as related to life satisfaction and development-related control beliefs. Others describe models and strategies for aging "successfully." Biomedical researchers address effects of successful or optimal aging on life expectancy and morbidity and distinguish successful from usual aging.[2]

Realizing that there may be no consensus about successful aging, we have organized this issue from what I believe is a patient's perspective. We begin by asking about the prospects for the prevention of acute and chronic diseases as we age. We know that the average life expectancy from age 65 is at least 19 years for women and 14 years for men.[3] The average life expectancy actually increases as persons survive to older ages. Thus, prevention and health promotion make sense at virtually any age.

In this issue, we also look at the major sources of age-related disability and morbidity from two perspectives. What is the nature of age-related decline and what are the prospects for modifying age-related decline? We also look at prevalent conditions associated with aging and ways that they limit optimal function or cause disability. Thus, we have asked authors to describe the possibilities to delay the onset of functionally limiting conditions or for minimizing excess disability associated with those conditions. In some instances, the answer may be, "There is not much that can be done" with, for example, macular degeneration per se. Nonetheless, there may be strategies for better adaptation or anticipating the inevitability of total blindness. Even though the content of the information may be discouraging to patients, most patients and their primary care physicians value the knowledge. In other instances—for example, living with osteoarthritis—patients and their primary care physicians may be pleasantly surprised by the opportunities to regain function.

The topics we have chosen are broad and include maintaining musculoskeletal and locomotor function, maximizing cardiovascular health, maintaining and restoring auditory and visual function, treating osteoarthritis, the use of medications, emotional health,

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maintaining cognitive function, and the importance of community resources in successful aging. We close with an article summarizing global interventions in a recent clinical trial designed to minimize the onset and effects of frailty.

Most patients want to maintain their well-being and minimize the effects of age-related decline. A few will ask us to help them achieve goals of high or elite performance into old age. Physicians need an information base to respond to these requests. Patients also seek advice on problems and disease—specific concerns related to aging. Most patients want to enhance function and maintain quality of life (or what social scientists call life satisfaction) in the context of a rising burden of age-related chronic diseases. Increasingly, physicians' jobs will be to manage and treat older patients seeking to live rich and productive lives in old age and with coexistent chronic disease.

Several themes are worth noting related to successful aging. Most will be interesting to our patients as well. First, longitudinal studies of changes in physical performance in older groups have shown patterns of both decline and improvement, thus suggesting that older age is not inevitably associated with decline.[4] Second, productivity can remain surprisingly high and may also improve with aging.[5] More than 90% of older adults do some productive activity. Catastrophic illness, especially stroke, can have a drastic effect on productivity. Psychosocial factors like life satisfaction and change in mastery also play an important role in productivity.

Another theme that appears repeatedly in the literature is the importance of moderate to strenuous exercise and the role of emotional support from social networks in predicting better physical performance.[6]

I am particularly impressed by the frequent disparity between disease severity and functional impairment that we see regularly in everyday clinical medicine. This phenomenon has been recently demonstrated in a study of the relationship of coronary artery disease severity and functional impairment that concluded that the relationship "is not as strong as may be assumed."[7] The study results suggest that at mild to moderate levels of disease severity and organ impairment, functional status is likely determined by a complex combination of biomedical and psychosocial factors, whereas in more severe disease, biomedical factors predominate. Modifiable psychosocial factors such as depression and anxiety, self-efficacy and quality of social support likely play an important role.

Physicians also play an important role in successful aging. We can be risk factors if we encourage too much bedrest and inactivity and thereby promote deconditioning. We are also (by definition) the cause of iatrogenesis, especially if we practice excessive polypharmacy and cause avoidable adverse drug reactions. This issue of THE WESTERN JOURNAL OF MEDICINE aims to help physicians become *protective* factors for successful aging in the way we practice (by avoiding iatrogenesis, of course) and the behaviors we promote, including encouraging conditioning and avoiding risk factors. Our older patients frequently see their physicians many times a year. They look to their physician for guidance. The role of the physician is crucial in achieving successful aging for many patients.

Even though there may be no generally accepted definition of successful aging, there is certainly much to be learned using successful aging as a heuristic for discussion. The knowledge base has considerable value for physicians and patients, although most researchers will characteristically note we still have "much yet to learn." As all readers are aging themselves, the value of learning about successful aging will serve the professional reader doubly—as a person and as a health care professional.

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SUCCESSFUL AGING

Ways to Make "Usual" and "Successful" Aging Synonymous

Preventive Gerontology

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Preventive gerontology is the study and practice of those elements of lifestyle, environment, and health care management that will provide the maximal longevity of highest quality for individuals and the population. As such, it focuses on a personalized hygiene agenda that varies in its emphasis according to a person's age, sex, and risk factor profile. It includes a matrix of strategies relating to diet, exercise, and the avoidance of substance abuse and adverse environmental exposure. Preventive gerontology carries differential emphases according to the life stage of a person, featuring long-term, low-cost, and low-risk lifestyle strategies in youth and middle age (generally to age 75) and more short-term, low-risk interventions in old age (>75), especially secondary prevention, according to individualized estimates of risk, cost, and benefit. The aggregate effect of widespread application of this approach—especially insofar as it is coupled with a rising level of education and continued psychosocial development—will be progressive congruency between usual and successful aging. A by-product will also be an ever-advancing median age of the population and, inevitably, a growth in long-term health and social service needs. Responsible planning for this consequence of success in the 21st century will require a rededication of North Americans to care for those in need regardless of age.

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The demographic imperative of an aging society is progressively capturing the attention of the North American public, its social and health care providers, and all who will consume and finance social and health care. Thus, the prospect of a progressive increase in average longevity, coupled with the successful aging of the post–World War II "baby boom" cohort, the relative dearth of support of aging baby boomers by those of the succeeding "baby bust" generation, and the inevitable rise in social and health care resource requirements of the growing number of elderly persons, has served to define the debate over the benefits versus the cost of increasing survival into old age. As a result, with the impending end of the 20th century and the ever-increasing aging and longevity of North Americans through at least the first half of the 21st century, intense yet mixed feelings about the future of the nation and its growing number of older citizens are expressed. Is there any way for average human longevity to increase without also increasing the burden to the younger generation in the workforce of caring for their aging parents and grandparents?

Aging, Natural Death, and the Compression of Morbidity

An optimistic answer to the above question captured the imagination of the readers of The New England Journal of Medicine in an essay in 1980 by James Fries, MD, a noted Stanford University rheumatologist, titled "Aging, Natural Death, and the Compression of Morbidity."[1] This essay inspired the concept of "preventive gerontol-

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ABBREVIATIONS USED IN TEXT
HMG CoA = hydroxymethylglutaryl–coenzyme A
LDL = low-density lipoprotein

ogy," first articulated in 1983.[2] In the present treatise, I will review the original premises of preventive gerontology, its principles and practice, and the evidence in support of its application accumulated to date, notably that generated during the past decade. I will also outline the inevitable and unavoidable "downside risk" of successful preventive gerontology if widely practiced—that is, the increased burden imposed by an older and more vulnerable population of survivors on older persons themselves, groups of older citizens, families who provide support for aging parents and grandparents, and society as a whole. The purpose of this review, therefore, is a critical appraisal of the cost and benefits of the widespread application of the principles of preventive gerontology. I hope that this review will reinforce—with full disclosure of both the risks and the benefits—the social contract by all North Americans to care and provide support for their aging members, both now and in the future.

In his initial thesis,[1] as subsequently amplified and recently reviewed,[3,4] Fries noted the progressive "rectangularization" of the US survival curve (Figure 1). He contrasted the curve in 1900 with that in 1980 and both in turn with that sometime in a future "ideal state," at which time, except for unavoidable premature losses attributable to trauma, including wars and natural disasters, maximal average human longevity would have been achieved. Thus, the maturation of any society—characterized by progressive industrialization and associated higher levels of prosperity that afford better housing, transportation, public health, sanitation, nutrition, education, and health care—has consistently been associated with decreased neonatal and pediatric mortality, usually attributable to reducing the incidence of death from infectious diseases and malnutrition. This has in turn allowed a progressively increasing proportion of those born to survive into adulthood and, indeed, into middle and even old age (defined as beginning at about 75 years). Comparing the US survival curve in 1900 with that in 1980, Fries estimated that of the increase in average human longevity possible for our species, by 1980 we had come 80% of the way (the ratio of areas between the 1900 and 1980 versus 1980 and "ideal" curves being 4 to 1).[1] By the same token, charting trends in increasing longevity in the United States since 1900 from birth, from age 20, and from age 65 led Fries to project that by the middle of the 21st century, maximal average human longevity in this country would become stable at 85 years of age. At that point, a histogram depicting the ages of death in North America would appear (Figure 2), showing only a tiny fraction of those born dying before old age, with a sharp mode in age at death at 85 years and a narrow gaussian distribution about that mode (±4 years). Thus, according to statistical principles, in the ideal steady state, 95% of those born would die between 77 and 93 years of age (±2 standard deviations), a small proportion (<1%) would survive to 100 years, and the absolute upper limit of the human life span would remain fixed at about 120 years (currently established by a French woman named Jean Calmonde who died at the age of 122 on August 4, 1997). This projection contrasted significantly with the histogram of ages of death in the United States at that time, which showed a mean age of 73.4 years, a standard deviation of 18.1, and a pronounced negative skewness. Already at that time, however, the modal age of death in the United States exceeded 80 years.

Consistent with the large proportion of the population surviving until the average age at death of 85 projected at

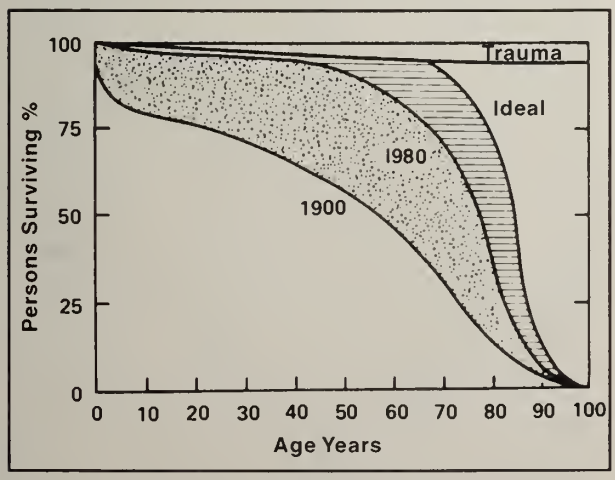

Figure 1.—The North American population survival curves are shown for 1900, 1980, and, in a future ideal state (from Fries[1]).

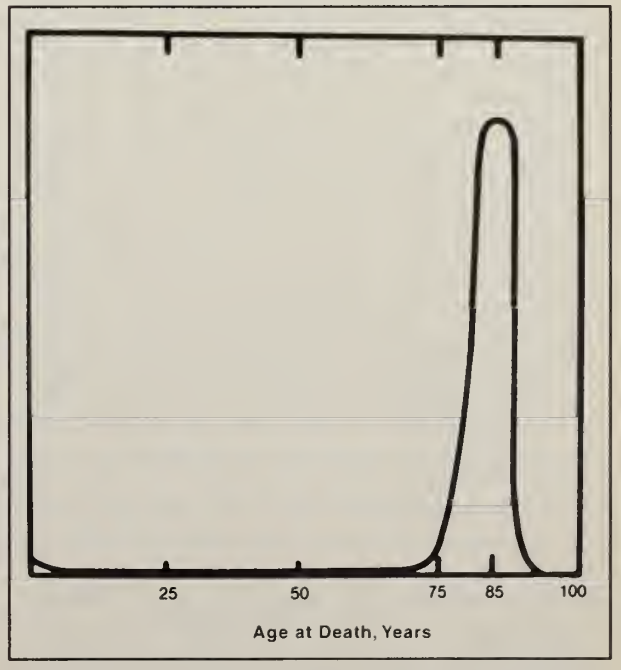

Figure 2.—A histogram of ages at death is shown for North Americans in a future ideal state (from Fries[1]).

steady state. Fries expanded on this thesis to provide the fundamental rationale for the concept of "preventive gerontology." This rationale focused on a single principle: if the disease processes causing premature death can be clearly identified and retarded through specific interventions, then avoidable or delayable death can be minimized, allowing "natural death" (from multiple organ system failure) to occur at the age genetically programmed for a person and, in the aggregate, for the species.

In illustrating this principle, Fries and Crapo elaborated a short list of "nonmodifiable aspects of aging" (reflecting "primary aging"), such as increasing arterial wall rigidity, cataract formation, graying hair, thinning hair, decreased kidney reserve, and diminished skin elasticity.[3] This was compared with a longer list of "markers of [secondary] aging," such as decreased cardiac reserve, dental decay, increased systolic blood pressure, decreased pulmonary reserve, decreased glucose tolerance, increased serum cholesterol level, decreased physical endurance and strength, osteoporosis, increased reaction time, decreased memory, and accelerated skin aging, all of which could be modified through alterations in lifestyle, the environment, or both.

A review of the "nonmodifiable" list in 1997 suggests that, by current standards, even Fries and Crapo were unduly pessimistic. For example, the assumption that increasing arterial wall rigidity is inevitable with aging has been challenged by the finding that such rigidity may be due to age-associated systolic hypertension and that this, in turn, is attributable to a diet high in saturated fat and sodium and a sedentary lifestyle. Similarly, cataract formation has been attributed as much to a lack of protection from damaging ultraviolet rays and consequent lens protein oxidation as to the aging process per se. Declining kidney reserve may be attributable more to a diet high in protein—and the nephrotoxicity of the nitrogenous waste generated—than to aging, and a declining elasticity of skin also may be traceable principally to the effects of ultraviolet light. Changes in the elasticity and appearance of aging skin may also be retarded or even reversed through the application of agents such as tretinoin. Finally, chemical approaches to the thinning of hair, largely hormonally driven, have been widely employed by men, and gray hair is increasingly uncommon among older persons, both men and women.

Most of these trends in US society to ameliorate the effects of aging represent more a tribute to the ingenuity and marketing skills of an entrepreneurial business community capitalizing on the preoccupation of North Americans with looking as young as possible than to any fundamental alteration in the aging process. The effects of aging on attributes associated with advancing chronologic age, heretofore assumed unchangeable, are becoming a subject for legitimate gerontologic investigation and pharmacologic and cosmetologic interventions.

Nevertheless, the contrast between that short list of nonmodifiable aspects of aging and the much longer list of "modifiable markers" remains clear. What also becomes evident from inspecting the latter list is the highly redundant nature of the short list of possible interventions and their multiple effects on those modifiable aspects. These coalesce through substantial synergisms in a multifaceted strategy that focuses on the following aspects (Table 1):

- Alterations in diet—matching caloric intake with caloric expenditure in a diet low in fat, salt, simple sugars, and cholesterol and high in complex carbohydrates;
- Exercise—emphasizing that which both consumes calories and builds strength;
- Controlled exposure to toxic substances—notably through avoiding inhaled or absorbed tobacco toxins, excessive alcohol intake, and illicit substance abuse; and
- Limited adverse environmental exposures—notably to excessive ultraviolet irradiation and toxic substances in the air and water.

When practiced on a lifelong basis, these interventions, nearly all entailing considerable personal choice and discipline, should prolong the period of adult vigor and reduce the prevalence of premature morbidity and mortality. These measures, together with the age-old admonition to "use it or lose it" through training and practice, represent the basic tenets of preventive gerontology.[2]

The fundamental goal of preventive gerontology, therefore, is to retard time-related processes, focusing especially on those that when accelerated result in premature morbidity and mortality. An approach to atherosclerosis prevention provides the quintessential example of this principle (Figure 3), although osteoporosis, senile dementia of the Alzheimer's type, and other examples of age- and time-related, chronic, multifactorial, and progressive disease processes could readily be listed. If such a strategy proves successful, the clinical horizon for any targeted disease process should be crossed at or near the upper limit of a person's genetically programmed life span. Such an outcome would, at least in theory, shorten the period between passage of the clinical horizon of disease and ensuing death, thereby effecting a "compression of morbidity" as proposed by Fries.[1] In the optimal circumstance, death would supervene from a competing cause, and the given disease would never be clinically expressed during life. That is, it would remain subclinical and hence be prevented altogether. This, then, represents the basic definition of prevention as viewed from a gerontologic perspective.

Proceeding from these principles, the realm of reduced longevity amenable to alteration through the effective application of the principles of preventive gerontology may be likened to the area between the differing survival curves in Fries' original hypothesis (Figure 4). As the preventable or delayable processes of secondary aging are eliminated in this scenario, the residual ideal curve emerges, representing the pure effects of primary aging (aging that is genetically deter-

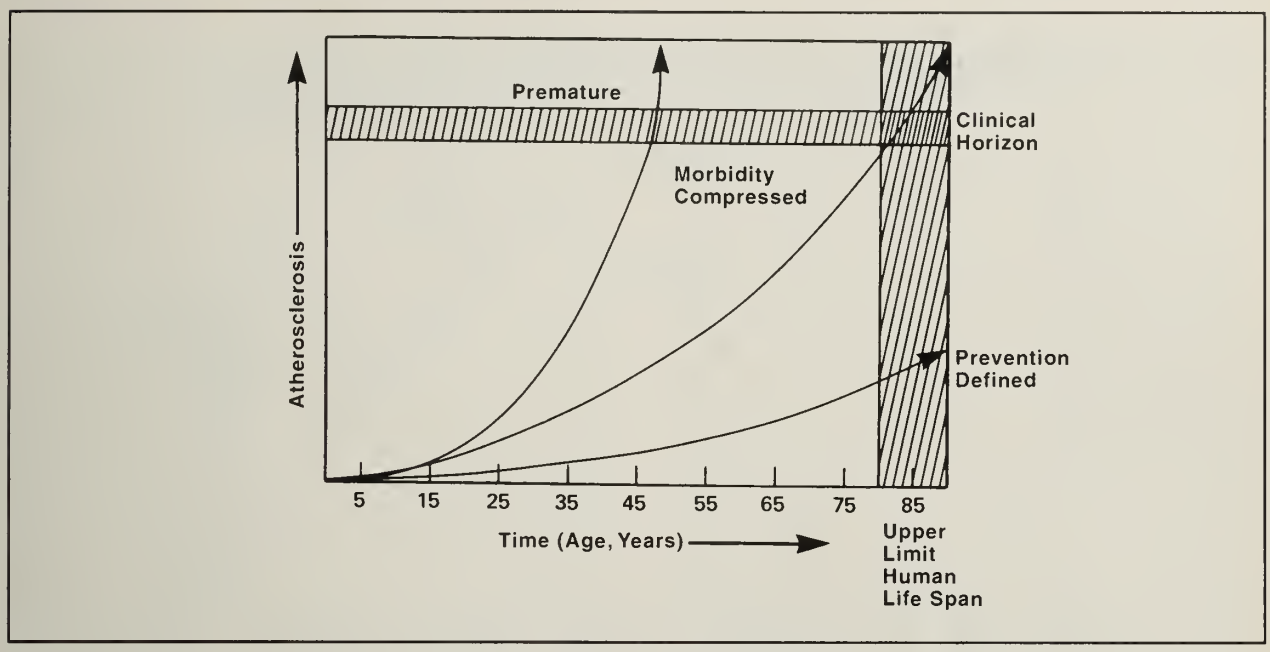

Figure 3.—The prototypical course of a chronic progressive disease—in this illustration, atherosclerosis—is shown in various scenarios according to differential success in applying prevention strategies (from Fries[1]). [Reproduced with permission from S. R. Bates and E. C. Gangloff, editors: Atherosclerosis and Aging. New York: Springer-Verlag; 1987, pp 75–103]

mined for the individual and the species and thus immutable in the absence of broad-scale favorable mutations). Thus, with the broad application of effective preventive gerontologic measures, geriatric medicine would become the field of caring for frail, elderly persons existing in precarious homeostatic balance, in whom a rapid terminal cascade of homeostatic chaos might be triggered by an insult (such as influenza) that would be withstood in a healthy younger person.

From this consideration, another principle of preventive gerontology becomes apparent: different intervention strategies are appropriate for different stages in the life span. Interventions most appropriate well before old age should be of an ongoing nature with payoff over the long term, whereas those initiated in old age must have short-term payoff. As a corollary to this principle, in terms of extending longevity, the result of effective preventive gerontology is inversely proportional to the age at which such intervention is implemented. That is, the older the age at which an intervention is initiated, the shorter the expected increased average longevity.

Translated in still other terms, "preventive geriatrics"—as opposed to preventive gerontology, which should be applied before old age—should focus on "trigger events," accidents or other untoward stimuli that threaten the precarious homeostasis of frail elderly persons. One pragmatic mnemonic developed for preventive geriatrics targets "infections, infarctions, and infractions"—that is, infections such as influenza, tissue infarctions produced by thrombosis or embolism, and infractions as exemplified by accidents such as falls or iatrogenic complications of medical treatments. Another corollary of this differential approach to intervention by age is that given the impaired homeostatic reserve with advancing age: the older the subject, the greater the risk of any intervention. This applies to physiologic, pharmacologic, or even lifestyle alterations as apparently innocuous as changes in diet or patterns of exercise. Thus, the therapeutic index of almost any intervention narrows progressively with age, and null or even net adverse outcomes are not at all unusual in advanced old age. This reality, reminding practitioners of the physician's first adage, "above all, do no harm," underscores a critical philosophical dimension of geriatric health care: in old age, especially, the primary focus must be on added quality rather than simply the quantity of life.

Rebuttal to Fries

The reaction to the Fries hypothesis was immediate and remains so more than a decade later. Perhaps most emphatic was the outcry against its almost sole emphasis on prevention, with a lack of balanced attention to the need for therapy and support for those frail and disabled who survive into old age (in part as a result of their successful practice of preventive gerontologic principles at earlier ages). Thus, the narrow age distribution at death under the Fries projection invites the assumption that death in old age in the ideal state would be rapid and that the need for long-term care would be minimal in the compressed period of morbidity preceding death. As articulated forcefully by others,[5] such a focus risks a disaster of neglect in health care policy planning for geriatric care, principally long-term care, that must proceed

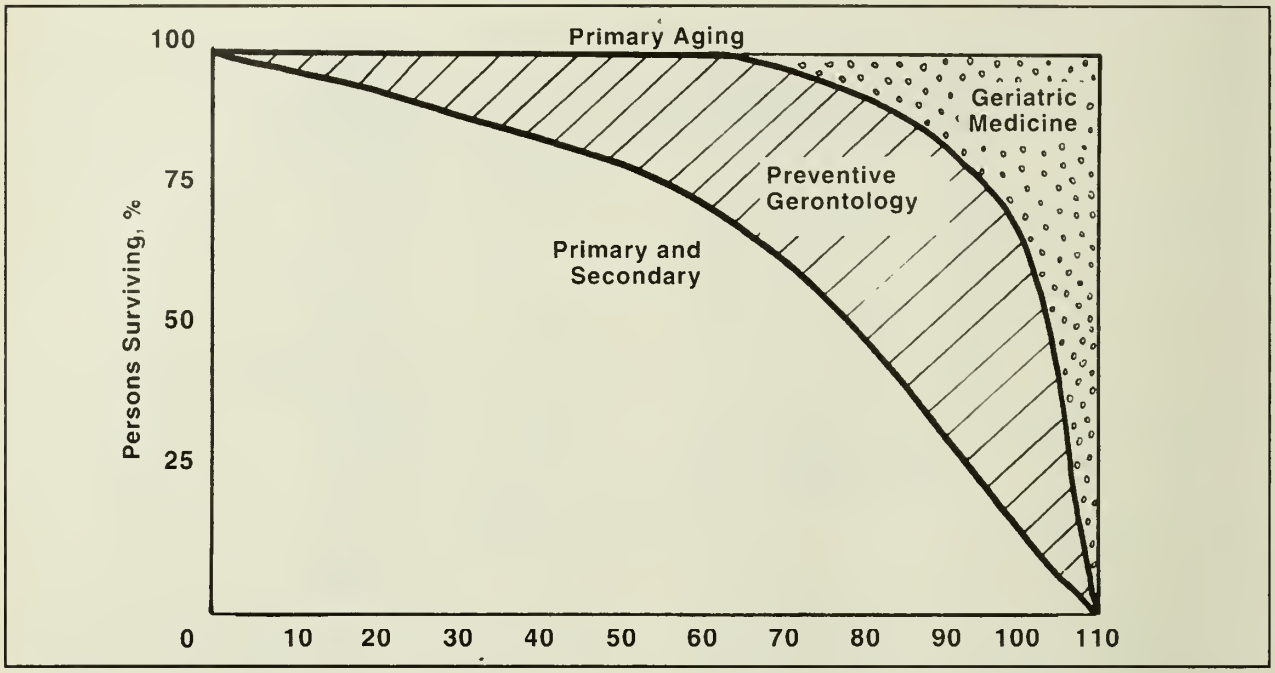

Figure 4.—The respective realms of preventive gerontology and geriatric medicine are depicted by analogy with the North American population survival curves (from Fries[1]).

in parallel with the progressive aging of the American population. Thus, an unavoidable by-product of successful preventive gerontology will be an explosion in the number of "oldest old" (>85) whose probability of requiring long-term care will increase exponentially with advancing age. Predicting and accounting for the consequences of that explosion are part of any rational public health policy planning process, including the development of the programs, professionals, and facilities that will be required and the dedication of necessary resources from both public and private coffers.

Just as ominous, the Fries scenario risks another flawed concept. Thus, although careful attention to diet, exercise, and other aspects of lifestyle and the environment may delay the onset of morbidity into late middle age or beyond, the age at death as a result may also be deferred by a substantial, perhaps nearly equivalent, amount. This would carry the potential for increasing rather than decreasing overall morbidity because of the development of other age-related diseases that would not have yet become expressed had death occurred at an earlier age. Indeed, evidence for any "compression of morbidity" to date is scant. Instead, a sober assessment of increasing average longevity in old age suggests a progressively greater proportion of the added longevity lived in a state of dependency, especially in women.[6] An extreme suggestion, for instance, has been that the only increase in longevity beyond age 65 over the past several decades has been in a state of disability and dependency. Perhaps a more balanced prediction is that the added survival will be equally distributed between states of independence and dependency, the relative proportions shifting toward dependency with advancing age. In other words, this is one downside risk of successful aging,[7] and developing a quantitative estimate of the expected addition in active (versus inactive or dependent) longevity from a population-wide implementation of preventive gerontology will remain an important objective for rational social and health care policy planning.

Finally, the Fries hypothesis suggested a fixed upper limit to the human life span (the "barrier to immortality") with no potential for increased average longevity beyond age 85. That this is not the case in an absolute sense has been amply shown by Manton and Soldo,[8] who pointed out that whereas mortality continues to decline at all ages throughout adulthood, this has been most dramatic in absolute terms in those older than 85. This may be an especially North American phenomenon, in which those beyond age 80 currently enjoy the greatest remaining longevity compared with both Northern European and Japanese cohorts.[9] Moreover, there is to date no suggestion that the progressive decline in morbidity is slowing. Indeed, morbidity and chronic disability rates among elderly persons have also been declining during at least the past 15 years.[10] Thus, the gloomy prognostication of many forecasters who have predicted a growing number of progressively frail old persons in the 21st century may have been unduly pessimistic. But whether this will translate into future elderly North Americans living into robust health until age 85 and then dying rapidly thereafter without a long period of decline and disability, a lá the Fries hypothesis, remains a source of intense debate, speculation, and skepticism. This suggests that, even under the most conservative projections, the need for

long-term care services, be they based in the community or in institutions, will grow progressively and dramatically at least through the middle of the 21st century as the number of old and very old persons in the United States grows exponentially.

Added Principles, Focus, and Considerations

In the intervening years since Fries' original thesis and the first introduction of the concept of preventive gerontology,[2] certain principles of preventive gerontology have been confirmed, others added, and the focus of attention shifted. Perhaps most dramatic has been the increased attention to the costs of effective prevention.

A cost-related principle is that a by-product of the effective prevention of premature disease is the increased risk of a given disease that might have passed the clinical horizon in middle age in the absence of applied preventive gerontology now doing so in old age—atherosclerosis, osteoporosis, and most chronic diseases in women. In like manner, a by-product of the effective prevention of premature disease is the increased risk of diseases passing the clinical horizon in old age but then accompanied by comorbidities. Some of such comorbidities may represent existing conditions already known to patients and physicians, whereas others that may have been subclinical now become manifest most often in the presence of acute illness. Examples of this are silent renal insufficiency that progresses to overt renal failure and subclinical cognitive deficits that become expressed as delirium in the setting of acute illness or pharmacologic treatment. Finally, a by-product of premature disease prevention is the increased prevalence and population burden of diseases that generally pass the clinical horizon in old age (notably Alzheimer's disease). Thus, a predictable consequence of interventions effective in preventing disease and death in middle age will be an epidemic of more complicated and more debilitating diseases and disabilities in the increasing proportion of North Americans who survive into old age—all adding to the cost of their care. Such increased longevity may conceivably be achieved at lower overall health care cost. As pointed out by others,[9] the current cost of caring for centenarians in their last five years of life ($1,800 per year in 1989–1990) was substantially less than for those dying at age 70 ($6,457 per year) because their costs both during and before their last years of life were low.

Also related to the cost-effectiveness of preventive strategies has been an increasing recognition in the past decade of the efficacy and efficiency of secondary prevention—that is, preventive strategies initiated after the disease passes the clinical horizon that reverse the process or delay progression. An example would be the prevention of recurrent myocardial infarctions or repeated osteoporosis-related fractures. Compared with primary prevention, such secondary interventions often need be of shorter duration and generally occur later in life and in the course of disease. They are also generally easier to implement, given patients' experience with, for example, a first infarct or fracture, making the explanation and definition of "acceptable risk" more understandable and explicit and patients easier to motivate. Such secondary interventions, however, often require costly approaches—high-tech procedures such as magnetic resonance imaging, coronary atherectomy, or carotid endarterectomy or expensive newly developed drugs such as hydroxymethylglutaryl–coenzyme A reductase inhibitors (HMG CoA ["statins"]) for reducing cholesterol levels and bisphosphonates for the prevention of recurrent osteoporosis-related fractures. Nevertheless, because of the concentration of attributable costs in those at greatest risk of disease events, such a secondary prevention strategy is frequently most cost-effective in terms of added "quality-adjusted" years of longevity.[11]

By the same token, perhaps counterintuitively, approaches to the primary prevention of chronic, age-related diseases that require the long-term application of relatively costly measures have received increasingly skeptical appraisal. For example, the use of cholesterol-reducing drugs in young women with hypercholesterolemia has been specifically questioned.[11] Such an expensive intervention over years to decades in a large number of women with moderate hypercholesterolemia at very low risk of myocardial infarction represents a huge cost of preventing the few infarctions that might occur in such premenopausal women. Hence, the emphasis in the primary prevention of age-related diseases has shifted to interventions of negligible cost (at least in economic terms), notably alterations in diet and exercise and the avoidance of toxic exposures (all cardinal features of preventive gerontology). A middle ground in the primary-versus-secondary-prevention debate has also been articulated: focusing on primary prevention in those at clearly increased vulnerability because of an adverse risk factor profile. This was specifically addressed in the National Cholesterol Education Program–Adult Treatment Panel II report,[11] and the rationale for targeted primary prevention of coronary disease in middle-aged men with hypercholesterolemia was confirmed in a recent West of Scotland pravastatin trial.[12]

Even as concern for the cost of interventions and secondary prevention has grown, the effectiveness and even cost-effectiveness of specific interventions have become apparent, validated through careful health services research. Perhaps of broadest contemporary attention has been the careful assessment of hormone replacement therapy in postmenopausal women as to the effects of such interventions on morbidity and mortality according to age at initiation.[13] The efficacy of postmenopausal hormone replacement therapy, notably for the prevention of cardiovascular disease morbidity and mortality (by ~50%) and osteoporosis-related fractures and mortality (by ~20% for hip fractures), has been widely validated. But even estrogen (plus progestin in women with intact uterus), initiated in the perimenopausal period at about

age 50 and taken indefinitely by all women, may increase average longevity by only about a year when taken for many years. This is because the generally acknowledged increase in the risk of breast cancer with estrogen use seems to rise with the duration of replacement therapy.[14] Once again, these considerations reinforce the importance that a preventive gerontology regimen should be tailored to individual risk assessment: for women at increased risk of coronary artery disease, long-term hormone replacement therapy seems clearly indicated; for those at increased risk of breast cancer, perhaps not.

Thus, a current focus of long-term, potentially costly, and troublesome interventions is on narrowing the number of patients being targeted to those at highest risk, thereby reinforcing the logic and efficiency of secondary prevention (such as in women with established coronary disease). Particularly encouraging among recent reports has been the demonstrated efficacy of reducing total (and, selectively, low-density-lipoprotein [LDL]) cholesterol levels by statin (HMG-CoA reductase inhibitor) drugs in preventing myocardial infarctions both in men with established coronary heart disease (the "4-S study"[15] and the CARE trial[16]) and in those without such disease but who are at an increased risk because of elevated LDL levels.[12] The simvastatin 4-S secondary prevention study was especially notable in demonstrating not only a reduced incidence of coronary events but also reduced total mortality, a goal not met in earlier cholesterol-lowering trials. Also encouraging, as more statin congeners enter the market and older agents move off patent, the cost of such currently expensive drug regimens will decline, placing this treatment within reach of more persons at high risk.

Other notable scientific advances since Fries' essay have also tended to validate the efficacy of intervention against risk factors to disease even at advanced ages. Most well known has been the Systolic Hypertension in the Elderly Program (SHEP), a random-allocation, placebo-controlled study in subjects of average age 72 (but including a substantial number older than 80).[17] This research clearly showed a reduced incidence of complications such as stroke and other manifestations of cardiovascular disease by the use of inexpensive antihypertensive medications. The study, designed, executed, and analyzed according to rigid clinical trial standards, showed the efficacy of blood pressure lowering, at low cost and with few adverse side effects, even among truly elderly persons. Even total mortality appeared to be reduced, at least marginally. Additional successful intervention strategies have been legitimized in elderly patients, notably long-term anticoagulant therapy for the prevention of strokes and other thrombotic complications in persons with atrial fibrillation[18] and valve replacement for patients with aortic stenosis, justified even in those in their late 80s. Thus, the accumulated experience of the past two decades has underscored the urgent need to conduct scientifically rigorous clinical trials in older subjects to investigate such important problems so prevalent in elderly patients as hypercholesterolemia, osteoporotic fracture–related events, arrhythmias, falls, and the like. To permit generalizing the findings of such studies to the practice of "real geriatric medicine" (what I have called "Realgeriatrik"), such studies must include subjects truly representative of persons of advanced age with their high prevalence of comorbidities and many areas of vulnerability.[19]

Other advances during the intervening decade have reinforced the principles articulated at the outset. For example, it has now been shown that stopping cigarette smoking is an effective preventative strategy even in old age. Of possibly nearly universal application, exercise has been shown to be an effective intervention even when initiated in advanced old age such as among nonagenarian nursing home residents, in whom improved functional ability and morale have been documented.[20] Such exercise regimens, especially when carefully initiated and supervised, can be expected to diminish cardiovascular disease morbidity and mortality to a substantial extent even among those older than 75 years, as suggested by carefully conducted epidemiologic surveys.[21] Given the possible effects of broad-scale exercise intervention programs, this expectation urgently requires confirmation in carefully designed, rigorously executed clinical trials. Once again, even such a powerful intervention will be predicted to have a progressively diminishing effect on expected added longevity with advancing age at initiation. Thus, although debate remains as to the immutability of the barrier to immortality posed by Fries at the upper limit of the human life span, increasing age is clearly associated with diminishing returns in added longevity from even the most efficacious interventions.

Hence, the preponderance of evidence published in the past decade supports the efficacy of intervention—primary, secondary, and tertiary—in forestalling or reversing the morbidity and mortality of age-related diseases at all ages, including very old age. Although much optimism has been generated by the research conducted to date, another sobering reality has emerged at the same time: more and more patients who survive an initial life-threatening disease complication present a second, third, or even fourth time with a recurrent event, and the cumulative burden of irreversible damage from such events is often end-organ failure no longer amenable to even the most invasive intervention (short of, perhaps, organ transplantation).[22] Hence, progressive disability and dependency may be the price of success even with access to and application of the best therapeutic interventions. This is perhaps most apparent in the case of cardiac failure, now the most frequent cause for admission to a hospital of Medicare beneficiaries. Not only has successful preventive gerontology deferred the onset of clinical coronary and hypertensive heart disease into old age, but the aggressive treatment of such disease, once expressed, permits the survival of an increasing proportion of the afflicted into advanced old age, all contributing to the cost of health care in elderly persons.

At the same time as the research-based underpinning of the principles of preventive gerontology has been

growing over the past decade, acceptance by an eager, health-conscious, and aging North American public has been growing even faster than the evidence would justify. Thus, powerful secular forces influencing personal behavior on a broad population-wide scale threaten to overwhelm the development of a scientifically rational approach to preventive gerontology based on deliberate, critical testing of explicit hypotheses. Clearly, smokers are on the defensive and inhale largely al fresco, in private or in small, mostly socially shunned groups. Dietary choices are made self-consciously: a recent survey quoted on National Public Radio suggested that only 42% of adult Americans admit enjoying their food for its own sake. Exercise has been widely embraced as a social activity in vogue at all ages. Sun exposure is avoided and tanning socially suspect. Moderation in alcohol consumption has become the social norm (thanks in part to the effectiveness of such organizations as Mothers Against Drunk Driving). Thus, many health-related behaviors with major implications to gerontology, some with but many without clear scientific justification, are changing dramatically in an aging US society in the late 20th century.

Concomitantly, chemical interventions of low-cost and possibly widespread application are also sweeping the country. Aspirin is widely taken for preventing coronary artery disease and stroke, reinforced by carefully conducted, legitimate studies (such as the Physicians' Health Study[23] and the Nurses' Health Study[24]). Aspirin is also frequently taken even by those at low risk as a hedge against thromboembolic disease. Similarly, ingesting antioxidant vitamins to prevent coronary artery disease and cancer and in the hope of slowing the aging process has become widespread, advancing faster in its application than firm evidence justifies.[25,26] The small apparent risk of such interventions, however, coupled with their low cost (and probable placebo effect), has invited unquestioning acceptance by a willing public fascinated by health issues and reinforced by media that capitalize on that fascination. Readers of Aldous Huxley's Brave New World will remember "Soma," which was ingested at the first sign of possible illness by the citizens of that world ("a gram is better than a damn"). Soma may be the source of the 21st century! An interesting note is that the ingestion of megadoses of both antioxidant vitamins and other micronutrient and dietary supplements has been associated with higher health status in general, especially in older groups. Whether this is a real or a placebo effect, reinforcing the optimism that predicts greater longevity in general, is uncertain. It should also be recognized, however, that such use of chemical agents may in some consumers' minds substitute for more difficult approaches to disease prevention. (Moreover, the addition of a low-fat diet to cholesterol-lowering therapy with lovastatin may confer no additional cardioprotection because of an offsetting decrease in high-density-lipoprotein levels induced by the low-fat diet,[27] further reinforcing the use of drugs as an attractive alternative to hard lifestyle choices.)

Such preventive health practices, both chemical and behavioral, are more prevalent among persons of higher socioeconomic status than among disadvantaged persons. This is clearly evident, for instance, in the greater use of postmenopausal hormone replacement therapy among women of higher socioeconomic and educational status. Thus, it may be questioned whether the apparent efficacy of such practices in physicians and others of high socioeconomic status represents a true cause-and-effect relationship or simply the well-known strong relationship between good health and higher socioeconomic status in North American and other western societies. At the other end of the scale, low socioeconomic status is strongly associated with poorer health and reduced average longevity all across the life span, and old age is no exception to this grisly contemporary reality. Such low-cost, possibly efficacious chemical and behavioral interventions may be as effective in those at the bottom of the socioeconomic scale in promoting health and longevity in old age (or, conceivably, even more so) if made universally available.

The net effect of all these observations and trends is that as the barrier to immortality of Fries is approached, whereas there may be diminishing returns in added longevity, there still is no clear evidence of an upper age limit to decreases in age-specific mortality. Of special interest to gerontologists, the sex differential in mortality, which broadened progressively throughout the first 80 years of the 20th century (reaching an age-adjusted peak of 1.8-fold higher in men than women in 1980) is finally becoming stable.[28] In the 1980s the increase in average added longevity for women was less than the increase for men, and hence the gender gap in average longevity narrowed slightly, a trend without precedent. Two alternative explanations have been offered to explain this narrowing. On the one hand, more and more women may be nearing their barrier to immortality (their average age at death in America already exceeding 80 years), thus retarding the trajectory of their added longevity. On the other, this may reflect the effects of such widespread behavioral change as reductions in cigarette smoking, which have been greater in men both in the rate of quitting and the degree of smoking, to the point where current rates of smoking are nearly equal in both sexes. What no research would suggest, however, is that changes in women's lifestyles over the past several decades, characterized most dramatically by their increased participation in the workforce, have had an adverse effect on their health or average longevity, the latter continuing to increase during this interval. This issue will clearly bear scrutiny in coming decades as more working women reach retirement age. Particularly ominous in this regard has been the purportedly greater prevalence of cigarette smoking, especially in young working women, and the progressive rise in the number of lung cancer deaths in women. Lung cancer has exceeded breast cancer as the leading cause of female cancer mortality since the mid-1980s (although the rates of lung cancer deaths are still lower than in men).

Secular trends that strongly discourage cigarette smoking, including major changes in workplace rules and social, legal, and economic forces, may largely nullify this threat to the health of both sexes in the near future. This would be predicted to narrow yet further the gender gap in longevity, with its heavy social cost in the loneliness and vulnerability of widowhood, increased dependency, and the greater requirement for long-term care of women than men that is a dominant feature of old age in the United States today.

Consequences to Society of Effective Preventive Gerontology

The cost of health care of the growing number of elderly persons has captured the attention of the public, and containing that cost has become a focus of intense political debate. The aggregate cost of health care in old age is one of the strongest forces behind the drive for health care reform. This is the case even though the proportion of expenditures for health care in the last phase of life is no greater now than it was two decades ago.[29] What has changed during that interval, however, is the number of persons of advanced age entering the final phase of life and the absolute cost of their care, which reflects the extraordinary inflation in health care costs in general of the past several decades. Of note, a widely perceived strategy to contain health care costs in the population at large—managed care—may or may not succeed in containing those costs while adequately meeting the needs of elderly persons. Careful analysis of the cost of providing effective care to Medicare recipients in a mature managed care organization (Kaiser Permanente, for one) has suggested that the time pressure for high primary care patient throughput may have decreased the threshold for specialty referrals and costly procedures and, paradoxically, increased the cost of care.[30]

Thus, the progressive aging of the population—to which effective preventive gerontology will clearly contribute—has become, together with the high costs of advanced technology, the principal force behind the continually escalating cost of health care in the United States and the public fervor to contain that cost. The corollary observation that effective prevention may increase longevity more than active life expectancy (that is, may prolong disability) has introduced ethical dilemmas of an unprecedented degree on a macro and micro level. As such, the progressive aging of the population and its inevitable association with increasing health care requirements have been the principal forces defining the emerging field of medical ethics. These have fueled widespread debate over respect for the autonomy of patients regarding their life or death wishes and even the consideration of physician-assisted suicide. These issues have driven debate and litigation regarding the other side of the issue as the pendulum swings to the opposite extreme: rather than assigning blame to physicians who may give insufficient consideration to patients' wishes to die with dignity, unduly prolonging life support.

Finally, what are the prospects that the average age at death in the United States will exceed the 85 years projected in the ideal steady state by Fries? Despite projections,[31] the continuing rise in average longevity in both sexes, the favorable outcomes of clinical trials in the elderly, and the continuing reduction in mortality in old age from such notable causes of death as coronary heart disease and stroke, the prospect for the average age at death in the United States to exceed 85 years at any point in the foreseeable future would seem remote. For that to occur, all causes of death in old age would have to be further reduced by more than 50% above age 60.[32] It is hard to conceive of such an outcome under even the most optimistic projections. Moreover, despite continuing declines in morbidity among very old persons over the past 15 years,[31] given the great increase in their number, their increasing average age, and the irreducible minimum of accumulated disability before death, the absolute need for long-term health and social services will continue to rise through at least 2050. Thus, admonitions remain[8]:

- The number of very old persons, notably women and especially widows, will burgeon at least through the middle of the 21st century;
- They will require much support, in both health care and social domains;
- This support must be provided principally by succeeding population cohorts;
- These cohorts will be of smaller size—at least until the baby boom generation has passed on;
- The need for long-term health care will progressively dominate the health care industry; and
- Debate over financing and personal and family responsibility for such care will preoccupy policy makers for the next half century.

To prevent such a scenario from destroying the moral underpinning of our nation, the social contract between the generations in this country will have to be reconfirmed. It is hoped that this will result in continuing rededication to society's commitment to increase the longevity and the quality of life for all citizens, preserving optimal vigor, self-respect, and self-determination regardless of age, but also guaranteeing care and support to persons of every age, which will be increasingly focused in the old, the very old, and the very very old.

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SUCCESSFUL AGING

Building Communities That Promote Successful Aging

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Despite the fact that, in a few years, a fifth of the US population will be older than 65 years and people will be living a third of their lives after retirement, we have developed few avenues that would permit older adults to play meaningful roles as they age and few institutions to harness the experience that older adults could contribute to society. In fact, older adults constitute this country's only increasing natural resource—and the least used one. In this article we consider the rationale for developing institutions that harness the abilities and time of older adults, rather than focusing solely on their needs. Such an approach would decrease the structural lag between a social concept of retirement as unproductive leisure and an aging population that is larger, healthier, and with a need for more productive opportunities. Gerontologically designed opportunities for contribution on a large social scale could well provide a national approach to primary prevention to maintain health and function in older adults.

(Fried LP, Freedman M, Endres TE, Wasik B. Building communities that promote successful aging. In: Successful Aging. West J Med 1997; 167:216–219)

The end of the 20th century is rife with major social fluxes. We live in an aging society in which, at birth, people can expect to live into their 70s and 80s, compared with their 40s at the beginning of the century. People are living longer, and they are living more of these years in good health. In the postretirement years, more than half of people aged 65 and older are now without disability, although 80% have one or more chronic diseases. Despite the much increased likelihood of living long lives, our society has not evolved its vision of what old age entails. Our social vision of aging no longer involves poverty and deprivation to the degree it did even 30 years ago. The prevailing social images of old age offer two major alternatives: fear of decrepitude, dependency, and relegation to a rocking chair, or at the other extreme, idealized images of limitless recreational time in a retirement community, often segregated from other age groups and the vicissitudes of daily life. In contrast to our social images, Eric Erikson and others have posited that the major developmental task that underlies successful aging is generativity—that is, defining one's life contributions and ensuring one's legacy through active participation in meaningful, contributory roles: the chance to "give back." And yet, there are few opportunities for older adults to engage in such meaningful roles or leave such a legacy in the postretirement years, and even fewer designed for having an effect at a scale beyond one-on-one interaction. This has been described as "structural lag,"[1,2] where the "norms, policies and practices are out of step with the demographic realities and policies of an aging society." To decrease this structural lag, we need to re-envision what successful aging in an aging society could mean.

Thus, there are few opportunities for older adults to serve their own developmental needs, and they are, in the main, marginalized from productivity while having a surfeit of time. In fact, retirement is occurring earlier and lasting longer than ever before, as more people, men especially, are retiring in their 50s. Among those aged 55 to 64, only 53% worked for pay in 1989, along with 22% of those aged 65 to 74 and 4% of those 75 and older.[3] During this period of retirement, older adults are, to a large degree, marginalized from productivity while having a surfeit of time. And yet, being able to make a contribution has been described as an essential element of "successful aging."[4] Consistent with this, it has been reported that women who participated in a voluntary organization or activity had greater longevity

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over a 30-year period than those who did not, controlling for age, their own education, and their husband's occupational status.[5] In a 2.5-year follow-up of the MacArthur Successful Aging study, participation in volunteer activities was predictive of improved functioning in older adults, with 32% lower risk of poor physical function in those so involved, independent of the effect of being active physically.[6] Casual or low-intensity involvements in such activities, however, may not confer these benefits. There is some preliminary evidence from this same study that the amount of time that one is involved in formal volunteering activities is important in conferring health benefits, with greater time involvement predictive of the level of physical functioning two years later (T. Seeman, PhD, Department of Gerontology, University of Southern California, Los Angeles, written communication, July 1997). In addition, there is evidence that organized behavior is among the best predictors of survival.[7]

Thus, in concordance with the theories of Eric Erikson,[8] it may be that successful aging is related to the opportunity to accomplish the adult development tasks of late life: integration and generativity. Defining and ensuring one's legacy is a core part of this task. According to Erikson, this is essential to psychological well-being in late life and, thus, to successful aging. It also appears that meeting these developmental needs, in some circumstances, may also confer health and functional benefits.

It is known that remaining active has health benefits important to successful aging. Physical and cognitive activity, along with social engagement (supports and networks), are related to improved health and function with aging. Regular physical activity, both of moderate and high intensity, are associated in older adults with lower frequencies of heart disease and diabetes mellitus, maintenance of weight, more beneficial levels of other cardiovascular disease risk factors, better physical function, and lower likelihood of disability and dependency.[4,6,9–11] Positive social supports and social networks are also independently protective of health and functioning as people age.[6] Social activity has also been related to improved health, functioning, and happiness.[12]

Some early research supports the "use it or lose it" admonition for cognition, as well as for physical activity; it may be that staying cognitively active helps protect memory as people age.[13,14] Therefore, remaining active physically, cognitively, and socially and making a contribution all appear important to health and well-being in late life. Some of these types of activities that are associated with better health may be difficult to accomplish in a retirement community setting or in isolation and, yet, may be highly important for successful aging in their own right. The consistency and intensity of involvement in such activities may also be necessary to affect the well-being of older persons.

This aging society is increasingly conscious of the need to find ways to help a population that is living longer also be healthier. Population-based and clinical methods are needed to develop optimal prevention and treatment modalities and thus reduce the number of years of late life lived sick and disabled. Such efforts should also help to decrease resulting health care costs and care needs. Researchers in clinical medicine and public health are actively engaged in defining the prevention and health promotion practices that will reduce the incidence of disease and prevent disability and dependency in older adults. In addition, we need to develop approaches for health promotion and primary prevention that might be available to older adults on a broad social scale. In part, this could be accomplished by creating widely accessible opportunities for older adults to remain active and productive.

This country has many other pressing social needs in addition to its aging society. One is the need to improve the outcomes of children in our society: their literacy, education, and personal well-being. In fact, the educational levels of children will be predictive of their future health outcomes as they become the next generation of older adults. Public schools, providing the education of most of the children in this country, are underfunded and overworked, needing more human capital to serve increasingly needy children while having less available for this important mission. Research data identify a particularly high-risk period: the progress of children to the third grade is a major predictor of their subsequent educational and occupational outcomes. Children who do not learn to read by the third grade are at risk for failure in school.[15] Undereducated families are ill equipped to support literacy activities in the home. Older adults could provide this support and the attention needed to teach young children to read. Also, many families with working parents have been faced with the problem of time famine. As a result of this, they have less time to work on literacy activities in the home. Many children would benefit from the presence and support of more adults and from more stability in their lives. Older adults could possibly offer some of this stability, caring, and consistency, which is essential to learning, as well as the richness of their experience and presence as role models. Older adults could provide social capital needed to directly support the educational needs and the outcomes of children. At the same time, older adults could be investing in the development of the well-educated workforce essential to the future stability of their own entitlement programs, Social Security and Medicare.

Thus, a possible area for creating generative opportunities for older adults is through creating meaningful roles for their serving in schools. This could provide a way to enhance successful aging through social programs, through generative institutions. Such an approach could also provide a new societal image of the opportunities and roles of people as they age, in this case playing unique and much-needed roles supporting the educational outcomes of children. If such roles were developed at a large enough scale and were designed for maximum effects on the needs of children in schools, the aggregate effect of a large number of older adults participating

nationally could be to support educational improvement on a population basis. The visibility of new, mature human capital supporting the well-being and learning of children in schools—through nurturing and enriching roles that do not displace paid workers but support their effectiveness—could offer an image for a positive, successful aging and a new, synergistic intergenerational social contract of the future. This contract is one in which the older generation are looked to, after retirement, to leave their legacy through strengthening the abilities of the younger generation. Such cultural generativity is developmentally appropriate for those who have completed their own child-rearing responsibilities.[16]

The key to having a substantial effect, simultaneously, in meeting unmet needs while improving the well-being of older adults on a population basis is to design programs that are attractive to older adults, support their effectiveness and maximize both their contribution and the health benefits and that are available on a large scale. One approach to this is currently being assessed in a pilot demonstration program entitled the "Experience Corps." This pilot program, in five US cities, places older adults in elementary schools to serve the needs of the schools and children using a unique gerontologic design to meet the goals described earlier. The elements of the model were drawn from gerontologic theory of what would produce maximum recruitment, retention, and effectiveness of older adults; from public health research of what would provide the greatest benefit of health and well-being of participants; from 30 years of experience in the most effective elements of existing senior service programs; and from the experience of small programs around the country in which older adults are assisting in schools. In the Experience Corps, older adults serve at least 15 to 20 hours a week to receive maximal health benefits and to allow them to take on meaningful roles in the schools and to ensure stability in those roles. Roles developed in this pilot program range as follows: from tutoring individual or groups of children in reading, mathematics, or computers and supporting the ability of teachers to meet children's needs by reading to small groups within the class, to developing enrichment programs for the children ranging from a people's court for conflict resolution or teaching socialized play during recess, to reviving and staffing unused school libraries, to programs that enhance attendance.

Roles are designed based on what a principal and teachers consider are their greatest needs and in collaboration with the school. To attract older adults to such intensive service, the adults receive an incentive of either a small stipend or in-kind benefits. The other essential, gerontologically supportive aspects of the program are that participants receive extensive training to extend their effectiveness in their roles. There is a supportive infrastructure for ongoing problem solving. Participants work in teams of six to ten for the greatest effectiveness and to augment their ability to solve problems too big for any one person to change by themselves. This arrangement also helps to develop positive social networks and support, and the members are able to fill in for one another in the event of illness. Enough teams are placed in a single school to make a visible difference in the school environment and to affect school outcomes. This pilot program, jointly developed and sponsored by the Corporation for National Service, Johns Hopkins University (Baltimore, Maryland) and Public/Private Ventures, with funding from the Corporation and the Retirement Research Foundation, is currently under evaluation to assess its feasibility and the short-term effect on the well-being of participating older adults. It has been successful in recruiting older adults, often from the neighborhoods the schools are in, with a commitment to improving the outcomes for the children in their communities. Retention and enthusiasm by both the participants and schools are high. Ongoing maturation of the model will, it is hoped, offer successful methods for generative roles that enhance outcomes for both the participating older adults and children that can be brought to a larger scale.

There is substantial validity to developing programs that would permit older adults on a large scale to help improve the educational outcomes of the next generation. Children in our society could benefit from a greater presence of older adults in their lives. The model of creating new, generative roles for older adults could be expanded to other areas of needs, as well—for example, in public health, the environment, or supporting independent living of other older persons. Meeting these needs could provide opportunities for increased activity, engagement, generativity, and social support for older adults, as well as opportunities to use their skills and gain new ones. Successful aging could well be enhanced by increased opportunity for "work that will outlive the self" and that "creates a legacy."[16]

Conclusion

We have an aging society that marginalizes older adults, limiting their ability to contribute their skills and time to our society. At the same time, the health and adult development needs of older adults include maintaining activity levels and engagement with others and having opportunities to "give back" and leave a legacy. With a declining support-dependency ratio and rising costs of entitlement programs for older adults, our society is becoming restive about the current social contract of entitlements without return contributions. These two strands of social change, along with unmet social needs, provide not just problems. They offer an opportunity for revising our social contract toward one of mutual benefit and engagement. We propose that health promotion efforts for older adults can meet social policy in the creation of meaningful service programs for older adults on a large social scale. One such demonstration, of a gerontologic model for high-intensity, critical-mass, senior service on behalf of children, is described above. This deserves replication. It could provide the backbone for making less intensive service more effective. It could also offer a model that

could be extended to large-scale programs in which older adults can help meet other social needs in public health, independent living, and the environment. Such generative institutions could facilitate the ability of older adults to leave a collective, as well as individual, legacy. Ultimately, large-scale opportunities for older adults to remain engaged in society and productive should enhance the health and function of our aging population.

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SUCCESSFUL AGING

Healthy Aging

A Women's Issue

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The life expectancy of women currently exceeds that of men by almost seven years, yet women spend approximately twice as many years disabled prior to death as their male counterparts. The diseases that account for death and health care utilization in older women (heart disease, cancer, stroke, fracture, pneumonia, osteoarthritis, cataracts) are also major contributors to disability. This paper reviews the scientific evidence that supports specific recommendations for older women that may prevent or delay these conditions for as long as possible. Risk factors for falls and fractures should be assessed and, where possible, modified. Adequate intakes of calcium, vitamin D, fruits, and vegetables should be encouraged. Weight should be monitored and weight loss discouraged for most women. Screening for B12 deficiency is recommended. Engaging women in a shared decision-making process about the use of hormone replacement therapy for longterm prevention of heart disease and fractures is important, as is regular screening for breast and colo-rectal cancer. Women should be encouraged to engage in enjoyable physical activities, including walking, for 30 minutes daily. These interventions have the potential to delay the onset and improve the course of many chronic conditions that prevail in later life.

(LaCroix AZ, Newton KM, Leveille SG, Wallace J. Healthy aging: a women's issue. In: Successful Aging. West J Med 1997; 167:220–232)

That women live longer than men remains one of the great epidemiologic and medical mysteries; yet, this fact is an ever-present reality in clinical medicine. Despite women's greater longevity, the health picture for older women is characterized by a disproportionate share of certain diseases and greater disability than in older men. In this article we describe the demographic and health characteristics of older American women with a view toward identifying the major public health and clinical challenges in this segment of the population; provide state-of-the-art summaries of the scientific evidence that pertains to the primary or secondary prevention of diseases that selectively afflict women, such as osteoporosis and women's cancers; discuss the use of hormone replacement for older women and the components of adequate counseling; and discuss the scientific evidence and its implications for making reasonable recommendations about nutrition and exercise to prevent the major health problems of older women.

The Demographics of Later Life: It's a Women's World

In 1992, the year of the latest figures on longevity, life expectancy among women of all races reached a record high of 79.1 years.[1] This compares with a life expectancy of 72.3 years for men of all races, also a record high. US women's life expectancy has increased by 31 years during the 20th century compared with a gain of 26 years for men in the United States. Among whites, women's advantage in life expectancy from birth narrowed slightly during the past 20 years, from a peak of 7.6 years in 1970 to the current level of 6.6 years in 1992. This is due to a more rapid decline during the past decade in mortal-

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ABBREVIATIONS USED IN TEXT

CI = confidence interval
RR = relative risk

ity rates among US white men than among other race-gender groups. African-American women have a life expectancy that exceeded that of African-American men by 8.9 years in 1992, which difference has remained relatively stable during the past 20 years. Figure 1 shows the percentage of men and women aged 65 years who survived to age 85 in 1950, 1970, and 1992, derived from US life tables.[1] Nearly half (49.4%) of women who achieved the age of 65 lived to be age 85 compared with less than a third (31.5%) of men aged 65 in 1992. For both sexes, the percentage of 65-year-olds living to age 85 has risen dramatically during the past 42 years.

Greater life expectancy underlies the rapid growth of the nation's older population. In 1990 persons aged 65 and older constituted 12.5% of the US population; by 2050 this group is projected to swell to 22.9% of the population. Similarly, those aged 85 and older constituted only 1.2% of North Americans in 1990, and their representation in 2050 is expected to grow to 5.1%. These segments of the population are disproportionately women; in 1990 there were 2.2 million women aged 65 and older compared with 841,000 men. By 2050 women aged 85 and older are expected to number 10.2 million, a figure approximately double that of men aged 85 and older.[2]

Unfortunately, women's longer life expectancy is accompanied by a greater number of years before death spent disabled. As shown in Table 1, among whites aged 65, remaining life expectancy is 19.3 years for women compared with only 15.5 years for men.[1,3] Women, however, can expect 2.7 of their added years to be spent with a serious limitation in their ability to do daily activities compared with 1.4 years for men.[3] Regardless of race and age, women spend about twice as many years disabled before death as their male counterparts.

Prevalence rates of disability are, in turn, higher among older women for all levels of severity of disability (Figure 2).[4] The 1994 National Health Interview Survey, Phase 1, shows the rates of needing help or supervision in activities of daily living (eating, dressing, bathing, toileting, transferring) to be about 3% among men and women aged 65 to 74, but these rates rise to 22.2% of women aged 85 and older compared with 14.5% of men.[4] The percentage of women needing help or supervision with instrumental activities of daily living (preparing meals, shopping, managing money, using the telephone, doing light housework) more than doubles across each ten-year age category for women, from 6.3% to 15.7% to 40.8% of women aged 65 to 74, 75 to 84, and 85 and older, respectively. In each age group, the rates of disability among women exceed those among men. The need to reside in a nursing home, perhaps the most serious form of loss of independence, is also substantially greater among women than men aged 75 and older, as shown in Figure 3 using data from the 1995 National Nursing Home Survey.[5]

Major Causes of Morbidity and Mortality in Older Women

Heart disease far exceeds any other chronic condition as a cause of death and hospitalization in US women aged 65 and older (Figures 4 and 5).[6–8] The rates of cancer and cerebrovascular disease are the second and third highest of the diseases that account for most deaths and

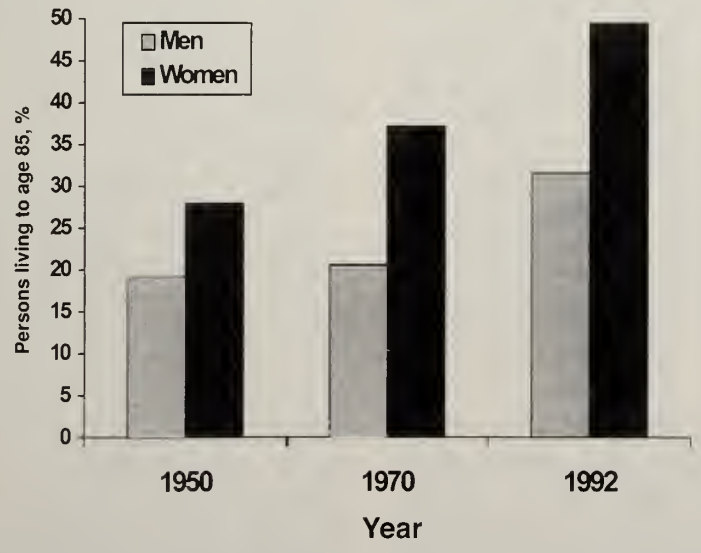

Figure 1.—The graph shows the percentages of 65-year-old men and women who survive to age 85 in the United States in 1950, 1970, and 1992 (from the National Center for Health Statistics).[1]

TABLE 1.—*Life Expectancy and Years of Disabled Life Among Americans Aged 65 and Older*†*

	Age 65		Age 75		Age 85	
	Life Expectancy	Years of Disabled Life	Life Expectancy	Years of Disabled Life	Life Expectancy	Years of Disabled Life
Women						
Black	17.4	2.8	11.4	3.0	6.3	3.2
White	19.3	2.7	12.2	2.8	6.6	3.0
Men						
Black	13.5	1.4	8.9	1.6	5.1	1.7
White	15.5	1.4	9.6	1.6	5.3	1.5

*From the National Center for Health Statistics.[1]
†From Guralnik et al.[2]

hospitalizations in older women. The rates of fracture climb steadily with age and rank second as a cause of hospital admission among women aged 85 and older.[8] Fracture reductions by far outnumber any other surgical procedure performed on women aged 85 and older. Pneumonia and influenza rates rank fourth among the major causes of death for older women. Pneumonia also accounts for a substantial number of hospital admissions, and the rates increase markedly with age.

The major reasons for ambulatory care visits by older women reflect both the precursors of the fatal and acutely disabling diseases noted earlier and several other aged-related conditions that cause substantial disability but are rarely, if ever, fatal. For example, hypertension and diabetes mellitus, two potent cardiovascular risk factors for women, account for more office visits than any other condition in women aged 65 to 79.[8] Osteoarthritis ranks third as a cause of office visits in women aged 65 to 69, fifth among women aged 75 to 79, and sixth among women aged 85 and older.[8] Cataracts rank second as a cause of office visits among women aged 85 and older and also rank high among women aged 65 to 84.[8]

The diseases that account for death and health care use in older women are also major contributors to disability. It follows that recommendations for healthy aging ought to be based on actions that women can take to avoid or delay these conditions for as long as possible (primary prevention). No less important, however, are recommendations that prevent the disabling and ultimately fatal consequences of these conditions (secondary and tertiary prevention). Fortunately, as we will describe, many interventions have positive effects at both junctures in the natural history of many conditions.

Prevention of Osteoporosis and Fractures

In the United States in 1994, more than 220,000 women were admitted to a hospital for hip fracture; the vast majority of these women were aged 65 and older.[9] As shown in Figure 5, the risk of having an osteoporotic fracture rises dramatically with age; women aged 80 and older are at particularly high risk. At the age of 50, a white woman's lifetime risk of fracture is estimated to be about 18% for hip fracture, 16% for spine or forearm fracture, and 40% for any of these three types of fracture.[10] Rates of fracture are lower among African-American women than among Latino or Asian-American women. Hip fractures are associated with a 5% to 20% increased risk of death in older women.[11] About half of women who suffer a hip fracture lose the ability to walk at least temporarily,[12] and between half and a third of older women are discharged from a hospital to a nursing home.[13] Osteoporosis and fracture are more common among women than men. This sex difference is largely attributable to a higher peak bone density in young adult men and to the occurrence of menopause in women that causes an accelerated period of bone loss for as long as several years.

The strong association of age with fracture risk is partly a function of the loss of bone density with age (Figure 6). The World Health Organization defines osteopenia as a bone mineral density that is between 1 and 2.5 standard deviations lower than that of young US white women and osteoporosis as a bone mineral density that is more than 2.5 standard deviations below that for a young adult reference group. By age 70 to 79, more than 90% of US white women are classified as having osteopenia or osteoporosis by this definition.[14]

The vast majority of hip fractures are preceded by a fall. Therefore, the fracture risk is influenced by risk factors both for low bone density and for falling. In addition to age, race, and ethnicity, risk factors for hip fracture include a maternal history of hip fracture, low body weight, smoking, deficiencies of calcium or vitamin D (or both), and excessive alcohol consumption. Risk factors that have been shown to decrease the risk of hip fracture include current and long-term use of hormone replacement therapy, walking for exercise, and current and long-term use of thiazide diuretics. Moderate alcohol consumption is not associated with an increased risk of fracture, and some studies show that bone density is actually higher among moderate drinkers.[15] The risk of falls is increased by older age, the use of long-acting benzodiazepines, the use of anticonvulsant drugs, lower extremity disability, poor distant depth perception, and an array

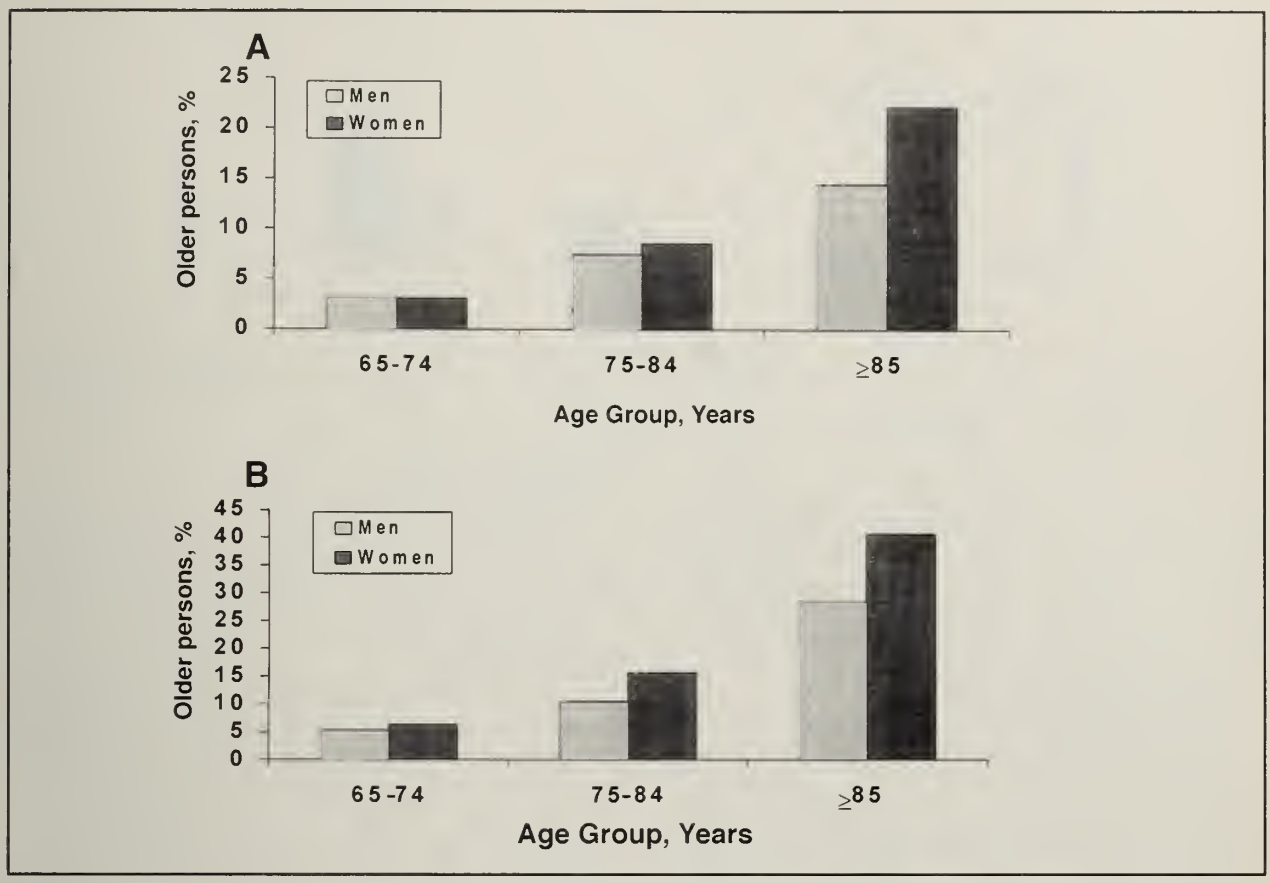

Figure 2.—The prevalence rates of disability in men and women in the United States (1994) are shown, A, in activities of daily living and, B, in instrumental activities of daily living (from the National Center for Health Statistics).[4]

of neurologic problems that cause gait disturbances—stroke, loss of palmomental reflex, and the like.[16]

The prevention of bone loss, falling, and in turn, the fractures that are a major cause of disability and health care use in older women should be regarded as a key component of promoting healthy aging. Worthwhile clinical interventions group well into the following categories: nutrition, physical activity, osteoporosis-preventing therapies, the avoidance of high-risk medications, smoking cessation, and fall prevention.

The area of nutrition and healthy aging will be considered comprehensively later. With respect to the prevention of osteoporosis and fracture, the rates of postmenopausal bone loss can be slowed by adequate intakes of calcium and the avoidance of vitamin D deficiency. According to the new August 1997 Institute of Medicine report, the recommended calcium intake for older women is 1,200 mg per day (the equivalent of 4 glasses of milk).[62] Many older women consume too little calcium to sustain their physiologic requirements. The average calcium consumption among American women is about 600 mg per day. It is important to encourage older women to assess their dietary intake of calcium and to either increase their dietary intake to reach the recommended targets for calcium intake or to increase their intake through dietary supplements such as those provided in some over-the-counter antacid medications. Vitamin D is necessary for calcium absorption. It is available in fortified milk and produced naturally in the body by getting 15 to 20 minutes of exposure to sunlight per day. For older adults who are homebound or in an institution or who have low intakes of milk, a multivitamin providing 400 IUs of vitamin D (600 IUs for people over 70) can be recommended to meet this requirement.

Weight loss during adulthood is a major risk factor for hip fracture. In a recent prospective study of nearly 10,000 older white women, the rate of hip fracture was 15 per 1,000 women-years among women who had lost 10% or more of their body weight since the age of 25 compared with 6.3 per 1,000 women-years among women whose weight remained stable; even lower rates of hip fracture occurred among women who gained weight.[17] Thus, the other major nutritional intervention that can contribute to reducing fracture risk is weight monitoring and avoiding weight loss. Although some studies have shown that high levels of caffeine consumption are associated with lower bone density and a higher risk of fracture, a recent study showed that even among heavy coffee drinkers, women who drank at least

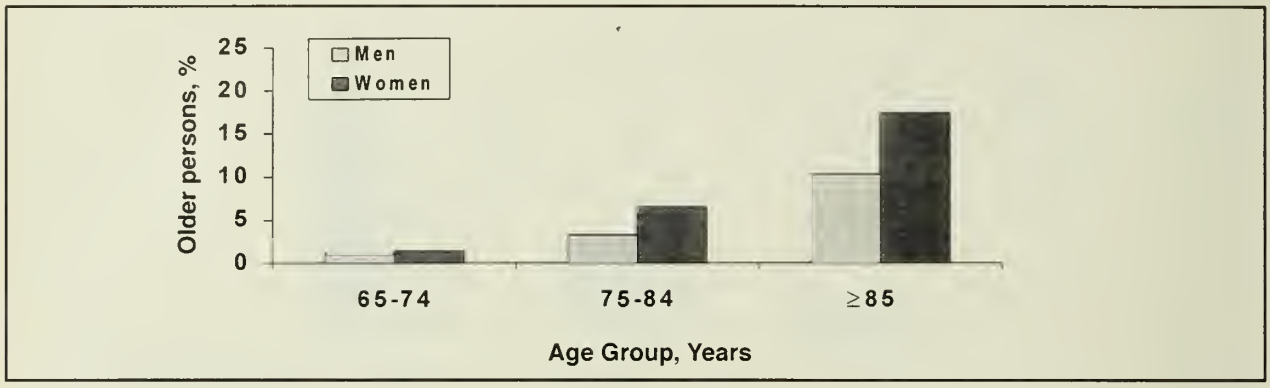

Figure 3.—The percentages of men and women in the United States living in a nursing home in 1995 are shown (from Guralnik et al).[5]

one glass of milk each day had bone density levels similar to those not drinking coffee.[18] As the second leading preventable cause of death in the United States, heavy alcohol consumption should be discouraged for many reasons, including an increased risk of falls and fractures. Women consuming small to moderate amounts of alcohol, however, can be reassured that it has no apparent effect on their risk of osteoporosis.

Both observational studies of hip fracture and randomized controlled trials of bone density and spine fractures have consistently shown that estrogen replacement therapy, with or without progestin, can reduce bone loss during and after menopause and reduces the future risk of fractures by about 25% to 30%.[19–22] In the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, women aged 55 to 64 who had never taken hormone replacement therapy before and women whose initial bone density was lowest gained the most density in the active treatment groups.[19] Thus, even if women have passed through menopause without taking hormone replacement therapy, the benefits of initiating it in later life are substantial with respect to lowering the risk of fracture. For the primary prevention of osteoporotic fracture, hormone replacement remains the preventive agent of choice for most women, but osteoporotic fracture is only one of many considerations in decision

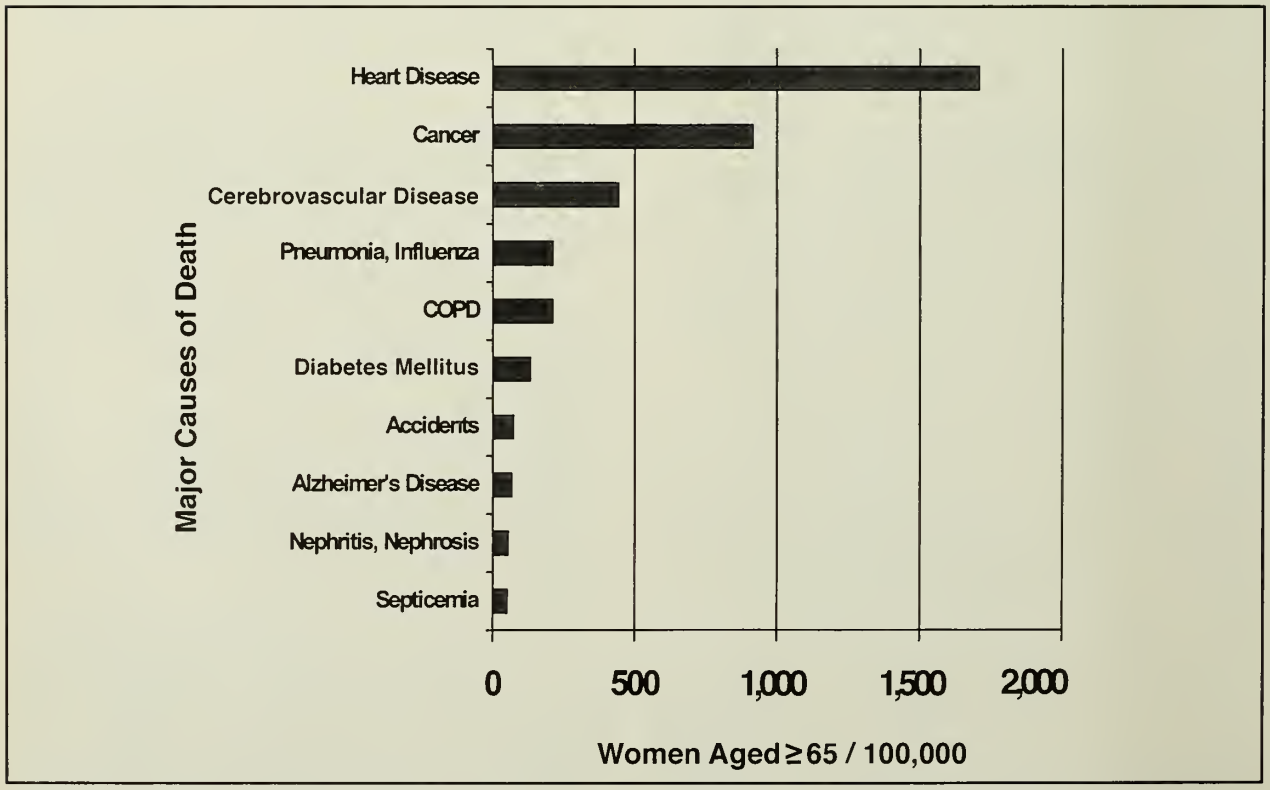

Figure 4.—The rates of the major causes of death per 100,000 in women aged 65 and older in the United States (1995) are shown (from Anderson et al).[6] COPD = chronic obstructive pulmonary disease.

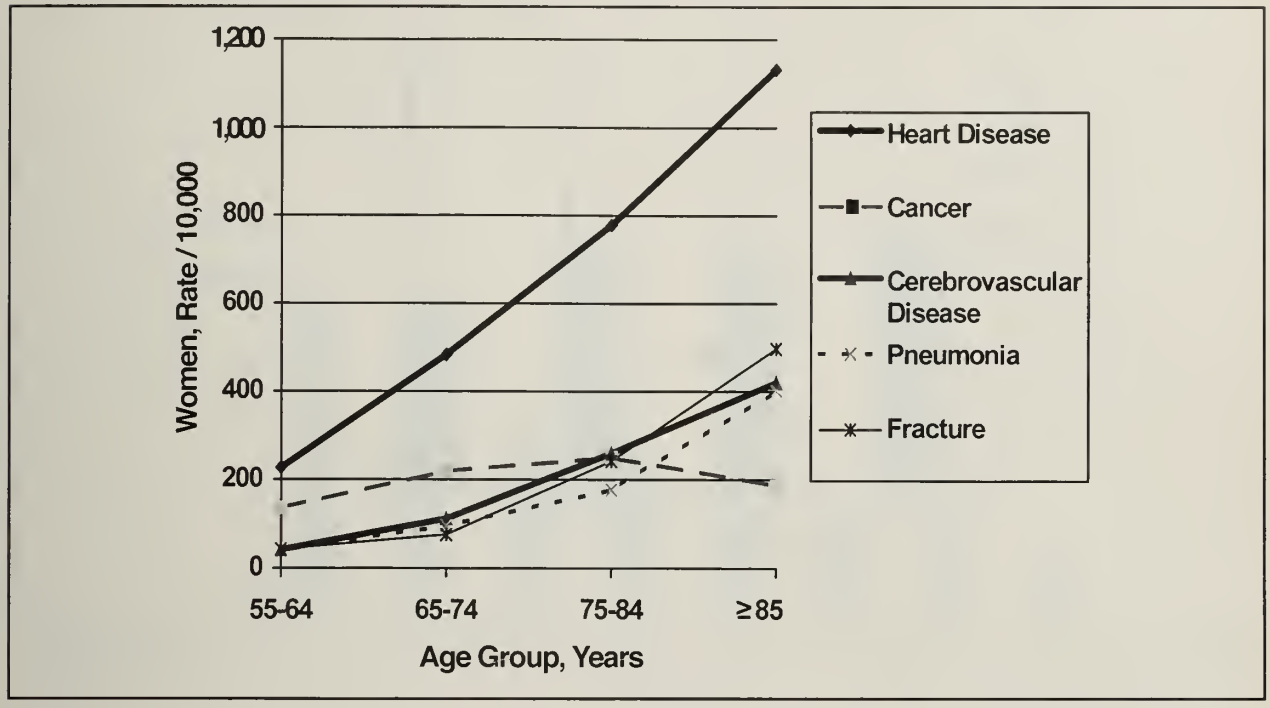

Figure 5.—The rates of hospital discharge for major diagnoses in women aged 55 and older in the United States (1991) are shown (from Cohen and Van Nostrand).[7]

making about long-term hormone therapy. This issue is discussed in detail in the next section. New drugs, such as alendronate sodium (and other bisphosphonates), are now available as alternatives for the prevention of fracture. Strong evidence exists that alendronate use increases bone density by about the same amount as hormone replacement therapy and reduces fracture risk, including hip fracture risk in women with vertebral fracture treated for three years.[23] Data are not yet available regarding the long-term risks and benefits of alendronate therapy for prevention or treatment. Thus, such agents should be used with caution beyond three years and the emerging scientific data on this and other new agents watched carefully for changes in the balance of risks and benefits.

Weight-bearing exercise is important for preserving health in many target systems including bone. Increasing physical activity reduces bone loss, the incidence of falls, and fracture risk in later life. Recommendations regarding physical activity are discussed in detail later.

Smoking is the leading preventable cause of death and disability in older adults. Reducing the risk of fractures is one of many reasons for advising older adults who smoke to quit. Unfortunately, for many older smokers, physician advice is not an adequate motivator for long-term behavioral change. State-of-the-art smoking cessation programs are based on behavioral change techniques that include tailored approaches to meeting individual needs, personalized feedback and support, and long-term reinforcement and follow-up. Clinicians should identify such programs in their health care environment or the community and strongly encourage older smokers to contact them.

Clinical interventions to reduce the risk of falling in later life can importantly alter fracture risk at a time when all women enter their years of greatest vulnerability to fracture by virtue of their diminishing bone density. A review of the prescription medications being taken by older people with a view toward reevaluating the need for sedative and hypnotic medications and polypharmacy is highly recommended. Other fall prevention strategies with proven effectiveness include gait training by a physical therapist for older people with gait problems or trouble transferring, balance and strength training as a component of a supervised (at least initially) exercise program, and home safety evaluations to remove environmental hazards and install safety devices such as grab bars and hand rails.[24,25]

The role of bone density screening for older women in fracture prevention guidelines is currently controversial. A bone density measurement contains information about future fracture risk that cannot be obtained from assessing the risk factors noted earlier. A recent meta-analysis of 11 separate studies showed that the risk of osteoporotic fracture was 2.6 times higher among women with bone density one standard deviation below their age-adjusted mean compared with women with higher bone density.[26] Despite strong evidence that bone density is associated with future fracture risk, there are no studies examining the value of bone density screening in reducing the future risk of fracture. Proponents of bone density screening argue that only by measuring

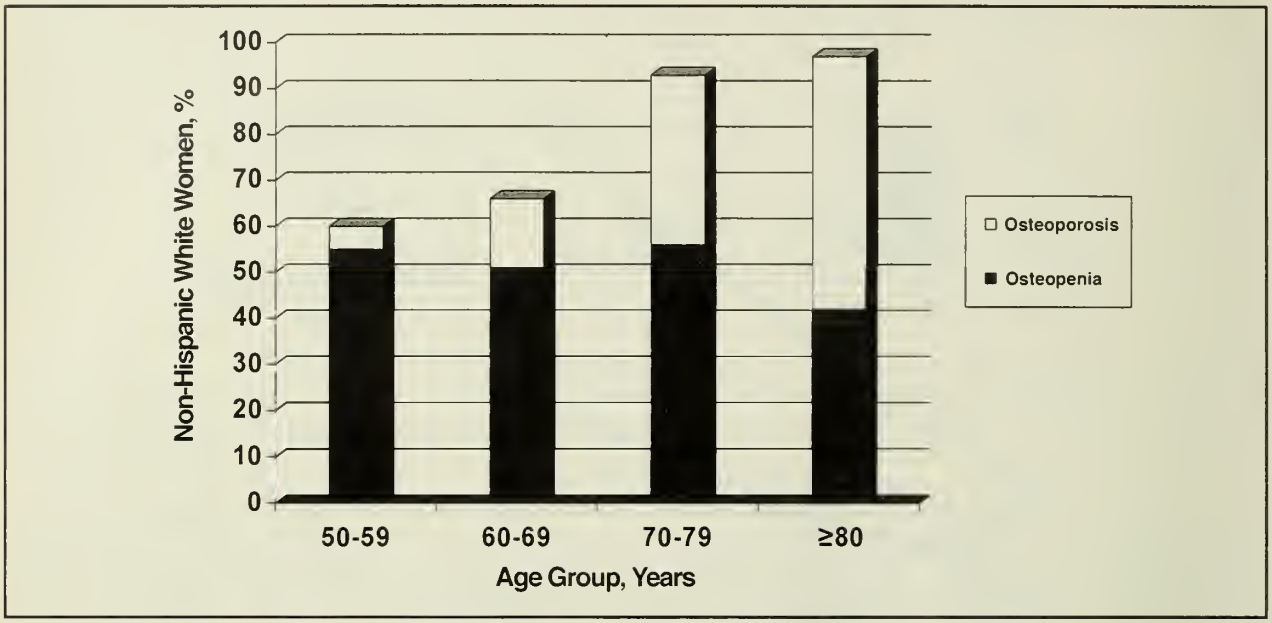

Figure 6.—The prevalence rates of low hip bone mineral density are shown by age for non-Hispanic white women in the United States, 1990 to 1993 (from Looker et al).[14]

bone density can preventive and therapeutic interventions be targeted to the women at highest risk, that the effectiveness of therapy can only be monitored if a pretreatment measurement of bone density is known, and that no other method is available currently for identifying women with high fracture risk due to osteopenia.[27] Opponents of widespread bone density screening argue that the evidence base is lacking for screening programs, that hormone replacement therapy can be recommended for preventing fractures and heart disease without knowing a patient's bone density, and that virtually all women aged 80 and older will be found to be osteopenic or osteoporotic (see Figure 6). An interesting development is that some preventive and therapeutic agents including estrogen replacement may increase bone density to a greater extent in women with low bone mass.[19] Thus, there appear to be situations when bone density testing can be useful both to women and their physicians. Such a situation is when a woman's decision about hormone replacement or other preventive therapies would be importantly influenced by knowing her bone density. The assessment of women with several nonmodifiable risk factors for fracture might also benefit from a knowledge of bone density because those women with high fracture risk and low bone density have the highest rates of hip fractures.[17]

Hormone Replacement Therapy Counseling for Older Women

In March 1996 the US Preventive Services Task Force published the following recommendation about hormone replacement therapy counseling[28(p829)]:

> Counseling all perimenopausal and postmenopausal women about the potential benefits and risks of hormone prophylaxis is recommended. There is insufficient evidence to recommend for or against hormone therapy for all postmenopausal women. Women should participate fully in the decision-making process, and individual decisions should be based on patient risk factors for disease, clear understanding of the probable benefits and risks of hormone therapy, and patient preferences.

This statement outlines the challenges and dilemmas surrounding hormone replacement therapy counseling. Whether or not to use it is one of the most complex and possibly far-reaching health care decisions of older women, and decision -making for hormone replacement therapy can serve as a focal point for discussing the major issues related to preventing chronic disease. The fact that hormone replacement therapy is of interest to older women is evidenced by the increasing rate of its initiation from 1994 to 1997 and the overall prevalence of its use among postmenopausal women at Group Health Cooperative of Puget Sound, Seattle, Washington (Figures 7-A and 7-B). Among women in their late 70s, the prevalence of hormone use was 20%, though its use is higher in the western United States than in other regions of the country.

Risks and Benefits of Hormone Replacement Therapy

The risks and benefits of hormone replacement therapy are summarized in Table 2. The evidence from randomized trials relating to its use to decrease the risks of osteoporosis and fractures has been discussed in the previous section. Meta-analysis of the results of 17 observational studies of the association between current hor-

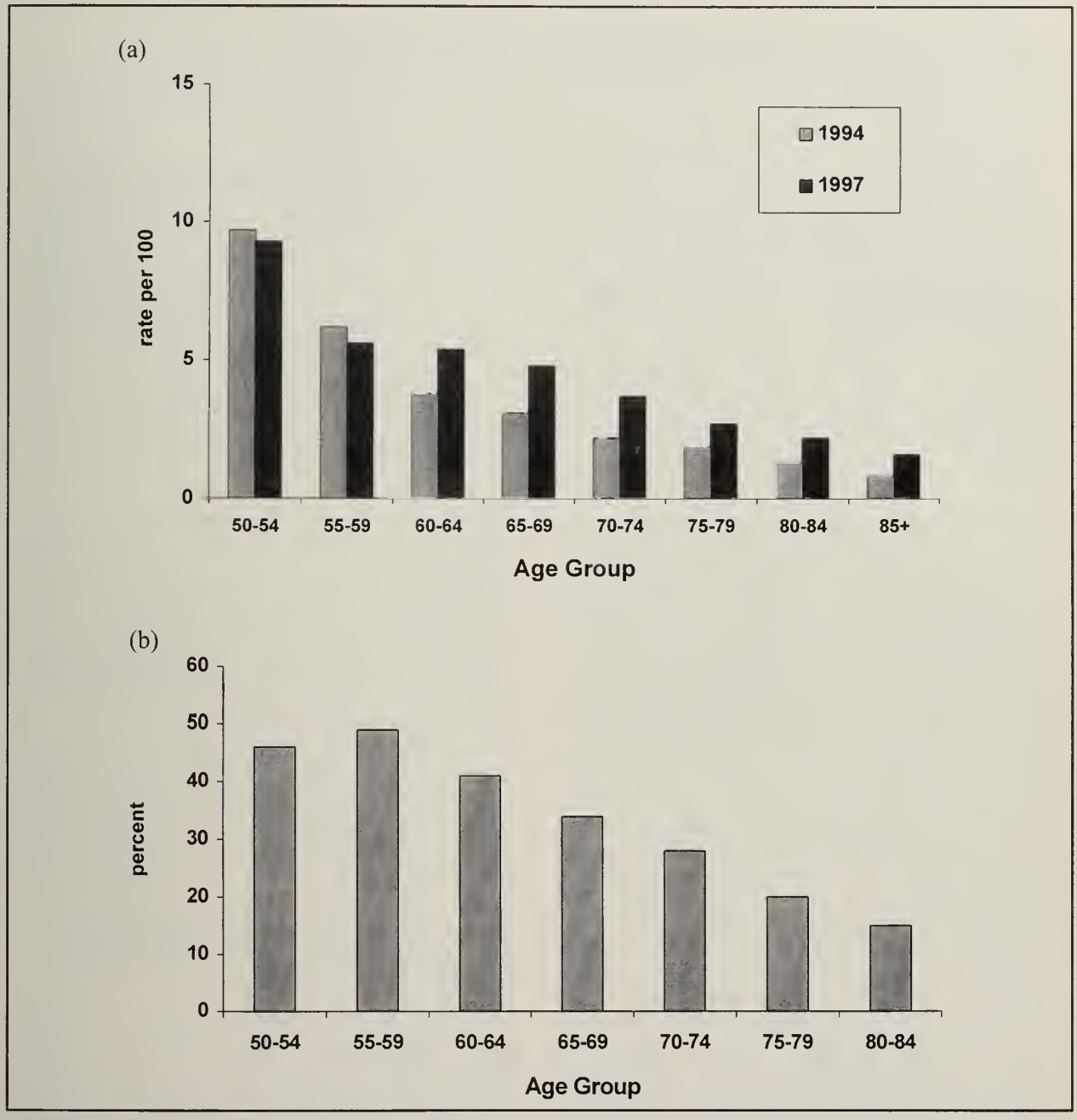

Figure 7.—The rates of hormone replacement therapy (HRT) use at the Group Health Cooperative of Puget Sound, Seattle, Washington, are shown: A, the rates of the initiation of HRT use in 1993–1994, and B, the prevalence rates of HRT use in 1996–1997.

mone replacement therapy and coronary heart disease in women yields an overall relative risk (RR) of 0.50 (95% confidence interval [CI], 0.45 to 0.59).[29] This association persists for estrogen replacement with or without progestin[30] and may be stronger with a longer duration of use.[31] Furthermore, hormone replacement therapy may reduce the risk of reinfarction (RR, 0.64; 95% CI, 0.32 to 1.30) and death (RR, 0.50; 95% CI, 0.25 to 1.00) among women who survive a first myocardial infarction.[32] And the twofold increase in the incidence of coronary heart disease risk seen in women with a surgical menopause (bilateral oophorectomy) is eliminated among women who use hormone replacement.[33] Past use, however, does not appear to be associated with a decreased coronary heart disease risk, regardless of the duration of use.[29,31] Despite the consistency of the evidence from these observational studies, there is lingering concern that a prevention bias may account for the strength of this association because women who use hormone replacement are generally healthier and more likely to participate in screening examinations than those who do not use it.[29,34]

TABLE 2.—*Benefits and Risks of Hormone Replacement Therapy (HRT)*

Benefits or Advantages	*Risks or Disadvantages*
Reduces risk for	*Increases risk for*
Osteoporosis and fractures	Breast cancer (current users with long-term use only)
Coronary heart disease events	Endometrial cancer (definitely unopposed estrogen, possibly long term >6 years of estrogen with progestin)
Gallbladder disease	
Relieves menopausal symptoms—hot flashes, night sweats, vaginal dryness and soreness	Monthly bleeding (cyclic HRT) or irregular spotting (continuous combined)
	Breast tenderness
	Headaches
	Taking pills daily, or following regimen
	Cost

Concerns about hormone replacement therapy center primarily on the increase in breast cancer risk observed with its long-term use.[35] In the Nurses' Health study, the relative risk for breast cancer among current hormone replacement users was 1.46 (95% CI, 1.22 to 1.74) for those with five to nine years' duration and 1.46 (95% CI, 1.20 to 1.76) for ten or more years of use; there was no increased risk for past use regardless of the duration of use and no increased risk for current use of less than five years' duration.[36] Results from a meta-analysis of 16 case-control studies also found a pooled risk estimate of 1.2 (95% CI, 1.02 to 1.51) associated with 15 or more years of hormone use,[35] and a second analysis combining the results of case-control and cohort studies of hormone use of eight or more years found a summary estimate of 1.25 (95% CI, 1.01 to 1.41).[37] Thus, breast cancer risks should be carefully evaluated when long-term hormone replacement therapy for prevention purposes is considered. Despite the increased risk of breast cancer with long-term hormone use, there appears to be no difference in the risk of death from breast cancer related to hormone replacement therapy.[37]

There is virtually no debate that the use of unopposed estrogen therapy yields a more than eightfold increase in endometrial cancer risk for women with a uterus[37] and that under almost all circumstances, women with a uterus should not use unopposed estrogen. A recent large case-control study showed an elevated risk of endometrial cancer among women using estrogen with progestin for more than six years.[38] If confirmed in future studies, this finding suggests that adding progestin to estrogen use does not permanently eliminate the risk of estrogen-induced cancer in long-term hormone replacement users.

Grady modeled the risks for endometrial cancer, breast cancer, coronary heart disease, and fracture associated with hormone replacement therapy to yield the lifetime probabilities of these diseases developing and the net change in life expectancy for a 50-year-old white woman treated with long-term hormone replacement.[37] The lifetime probabilities for women with and without long-term hormone replacement therapy were coronary heart disease, 34.4% versus 46.1%; hip fracture, 12.8% versus 15.3%; breast cancer, 13% versus 10.2%; and life expectancy was 83.8 years versus 82.8 years. This implies that the benefits and risks of hormone replacement therapy relate more to years lived free of chronic disease than number of years lived.

The evidence base for the risks and benefits of hormone replacement therapy is changing rapidly. There are active areas of inquiry, including colorectal cancer, osteoarthritis, Alzheimer's disease, and memory, where the evidence remains insufficient to offer much certainty of risk or benefit.

Physicians' Role in Hormone Replacement Therapy Counseling and Informed Decision Making

Physicians have a crucial role in guiding and informing a women's decision about hormone replacement therapy. When female health maintenance organization enrollees aged 50 to 80 were surveyed, physicians were cited as a primary source of information among 83.4% of current hormone users, 66.1% of past users, but only 30.6% of never users. Only 46.6% of never users had ever discussed hormone replacement therapy with their physician.[39] Similarly, 71.8% of current hormone replacement users reported that the amount of information from their provider about the benefits of hormone replacement therapy was about right, compared with only 47.4% of past users and 31.3% of never users.[40] The proportion of women who reported receiving no information about the risks and benefits of hormone replacement therapy increased from about 24% for women aged 50 to 59, to 53% in women aged 70 to 80 (Newton KM, LaCroix AZ, Keenan N, Anderson L, The influence of providers on women's

TABLE 3.—*Characteristics of Adequate Hormone Replacement Therapy (HRT) Counseling*

The woman will:

- Have an opportunity to ask questions and share her beliefs, expectations, and concerns about HRT
- Obtain answers to her questions in terms she can understand
- Have an opportunity to express her preferences
- Receive information or advice that helps her make a decision
- Leave the encounter with a clear plan of action

decision-making regarding hormone replacement therapy, January 1997).

Thus, it appears that older women would benefit from initiatives to assist them in making a shared, informed decision about whether or not to use hormone replacement. At a hormone replacement therapy counseling session, this involves assessing possible contraindications to the therapy, assessing menopausal symptoms and individual risks for chronic conditions that might be affected by hormone replacement therapy, relating how these conditions might be modified by the therapy, discussing options besides hormone replacement for reducing risks, and discussing options for hormone replacement regimens. Within the context of this discussion, the characteristics of an adequate hormone replacement therapy counseling session are presented in Table 3. Such a session may take as long as 20 to 30 minutes to complete, may require further assessments (for example, obtaining lipid levels or a mammogram), and concludes with a clear summary of the decision. Providing women with materials to help prepare them before the appointment may improve satisfaction with the decision making and reduce appointment times. One such aide that used a booklet, audiotape, and personal worksheet reduced uncertainty about the choice made and improved comprehension.[41] Other options include the use of workbooks, videotapes, books, and special classes.

Finally, any decision about hormone replacement therapy use should be reevaluated periodically. As the evidence base about chronic diseases changes and the results of randomized trials currently underway become available, both women and their physicians may need to revisit the decision and the factors on which it was based. Women's personal preferences, risk factors, and health status can also change as they age.

Optimal Nutrition for Healthy Aging

What we eat and do not eat and how long and well we live are viewed by many older adults as inextricably tied. Nonetheless, optimal nutrition is a challenging goal for many older adults because several risk factors for malnutrition become more common with age. These risk factors disproportionately affect older women and include depression, living alone, low income, the presence of multiple chronic conditions, and disability. One in five older adults skip meals daily, and only one in eight eat the recommended five or more servings of fruits and vegetables each day. Poor nutrition is a harbinger of poor clinical outcomes in older adults who have an acute health event and can lead to impaired immune function, slower wound healing, cognitive dysfunction, and anemia. In addition, the public pays great attention to weekly news reports in the hopes of learning which nutrients in certain amounts will prove to extend healthy life. Although the future may hold such breakthroughs, this brief section outlines a set of assessment and intervention activities that promote healthy aging based on current scientific knowledge.[42]

Weight, weight history, and weight relative to height are easily obtained measurements that contain much information about health status and nutritional adequacy. Weight losses or gains of 5% or more of body weight over a 6- to 12-month period should prompt clinical evaluation and intervention because they are associated with an increased risk of death and other morbidities, such as hip fracture. Another important assessment is the vitamin B_{12} status. The prevalence of vitamin B_{12} deficiency among older adults is estimated to be 5% to 15%. Routine screening is recommended because the signs and symptoms of vitamin B_{12} deficiency can be elusive. A serum vitamin B_{12} level is the recommended screening test. Levels above 260 pmol per liter (350 pg per ml) rule out the presence of vitamin B_{12} deficiency whereas levels below 110 pmol per liter (150 pg per ml) indicate deficiency. Levels in the intermediate range are difficult to interpret with certainty because about half of people within this range will be deficient in vitamin B_{12} at the tissue level, and the other half will not. In the presence of signs or symptoms that might be attributable to vitamin B_{12} deficiency, some experts favor treatment in this range. Alternatively, some advise obtaining serum levels of homocysteine and methylmalonic acid when B_{12} levels are indeterminate. These tests appear to be more sensitive and specific measures of B_{12} deficiency at the tissue level and can help clarify whether treatment with B_{12} is indicated. Last, assessments of the main physical and psychosocial risk factors for malnutrition (depression, social isolation, poverty, disability) should be part of the standard evaluation of older adults. Multivitamins and nutritional supplements can be recommended to improve nutritional status in those who screen positive. It is equally important to mobilize the health care team to assess the physical and psychosocial needs of the person and to arrange for the needed assistance.

The antioxidant vitamins C, A, and E are receiving much attention in trials aimed to evaluate their ability to prevent heart disease, stroke, cancer, macular degeneration, cataracts, and other age-related conditions. At present, there is insufficient evidence to recommend high-level supplementation with any of these vitamins to promote healthy aging. It is also unclear whether the best physiologic effects of these antioxidants come from dietary intake or supplementation, although many stud-

ies show lower rates of the aforementioned diseases in those consuming larger amounts of fruits and vegetables rich in these antioxidants and perhaps other important, as yet unidentified, micronutrients. Older adults can be encouraged to take a multivitamin as a means of ensuring adequate intake in combination with a diet rich in fruits and vegetables.

So what exciting dietary advice can be given to promote healthy aging? The best advice continues to be increasing fruit and vegetable intake to five or more servings per day, decreasing total fat intake to 30% or less of total calories, and decreasing the intake of saturated fat as a component of total fat, optimizing intakes of calcium and vitamin D to the recommended levels through diet, supplementation, or both, and increasing the use of daily multivitamins.

Physical Exercise for Older Women

Physical activity is one of the most important targets for promoting health in older women. Based on 1990 national estimates, only 24% of women older than 65 engage in regular exercise.[43] Among racial minorities and persons with less than high school education, the prevalence of a sedentary lifestyle is much higher than in whites and in those with more education. We know from many studies, however, that regular physical activity offers tremendous potential for reducing the incidence of disease and mortality risks and preventing disability in the later years of life. Further, there is mounting evidence that physician advice regarding exercise leads to increased physical activity.

Although many of the studies examining the benefits of physical activity were conducted in middle-aged male groups, newer evidence suggests that older women sustain many of the same exercise benefits as men. Results from the Framingham Heart Study showed that all-cause mortality was a third lower in women who exercised than in those who were least active.[44] With respect to cardiovascular health, results from a recent prospective study showed that walking more than four hours per week was associated with a 25% reduction in hospital admissions for cardiovascular disease in a group of healthy elderly women and men observed for four to five years.[45] In the National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Follow-up Study, the incidence of stroke was found to be significantly lower in white women who reported high levels of recreational or nonrecreational physical activity, after controlling for other risk factors.[46] Exercise benefits have been found for other chronic diseases, including reduced risks of diabetes mellitus, hypertension, bone loss and fractures, selected cancers, depression, and obesity.[17,47–49]

As noted earlier, women have the highest incidence of disability, and their rates of disability increase with age. Evidence from both observational studies and randomized trials shows promising benefits from exercise in reducing risks for disability in older women. Recent reports using population-based data have shown that physical activity reduces the risk for lower body disability in older women and men.[50,51] The Longitudinal Study on Aging found that moderate activity such as self-reported walking four to seven days per week was associated with a twofold reduced risk for lower body disability in whites and as much as a sixfold reduced risk in blacks compared with their sedentary counterparts.[51] Randomized trials involving exercise interventions have found reduced risks for falls,[24] improved strength,[52] and improved function[53] in older adults.

Results from randomized trials show that the benefits of exercise in the elderly clearly exceed the risks. As with younger persons, the importance of appropriate warm-up and cooldown periods for preventing exercise-related injuries cannot be overstated.[54] Gradual increases in the level of activity can safely build strength and endurance. The most common reason for stopping regular exercise is the occurrence of injury, so every effort must be taken to prevent injury when engaging in physical activity. More and more community exercise programs are being geared to the needs of seniors. Group exercise activities offer social advantages and group support for exercise maintenance, but home exercise can be better incorporated into daily schedules. Working with patients to help them identify barriers to exercise and to set goals to increase activity has helped to change behaviors. An extensive program, known as Project PACE, has been developed to guide physicians in counseling their patients to exercise[55] and is currently being tested in randomized trials around the country, with positive preliminary reports.[56,57]

The vast majority of older women patients could benefit from their physician's advice to begin or continue regular exercise. Current guidelines from the Centers for Disease Control and Prevention and from the American College of Sports Medicine recommend that all adults engage in 30 minutes or more of moderate-intensity physical activity on most, preferably all, days of the week.[58] The recommendations state that it is not necessary to do exercise for 30 minutes at one time, but that intermittent bouts of activity lasting as long as 10 minutes can be beneficial. As the risks associated with physical inactivity to the health of older women become more evident and numerous, the need for physicians to advise their older women patients to exercise becomes more urgent. The seminal work of Fiatarone and colleagues in which institutionalized nonagenarians participated in high-intensity exercise training showed that one is never too old to start exercising.[59] Older women and, in particular, those who are most at risk for the development of disability stand to gain the most from incorporating physical activity into their daily lives.

Early Detection of Cancers

After age 65, the incidence and mortality rates of cancer for US women are highest for cancers of the

TABLE 4.—*Rates of Cancer Incidence and Mortality in US Women of All Races Aged 65 and Older, 1990 to 1994**

Cancer Site	Incidence	Mortality
	Rate/100,000†	
Breast	443.4	125.6
Colon and rectum	256.6	107.1
Lung and bronchus	236.8	192.8
Corpus and uterus	100.5	23.0
Non-Hodgkin's lymphoma	64.6	35.4
Ovaries	57.9	43.6

*From Ries et al.[60]
†Age-adjusted rates, 1990 to 1994.

breast, colon and rectum, and lung and bronchus (Table 4).[60] For those few cancers that are detectable in a presymptomatic phase and where early treatment improves prognosis, regular cancer screening is an important component of promoting healthy aging. The notable gap between incidence and mortality rates for cancers of the breast and colon and rectum reflect the important results of early detection and effective treatments. Although a thorough review of the scientific evidence regarding cancer screening is beyond the scope of this article, the following recommendations are consistent with the cancer screening guidelines of the Group Health Cooperative of Puget Sound and are derived from a systematic review of the evidence pertaining to the effectiveness of population-based screening programs in improving health outcomes.[61] The recommendations all refer to asymptomatic women and not to those who present with any clinical signs or symptoms of cancer, who should be evaluated individually. Mammographic screening for breast cancer has been consistently shown to reduce breast cancer mortality among women older than 50 and is recommended every one to two years for all women. In addition, older women are encouraged to learn and practice breast self-examination on a monthly basis and to have a yearly breast examination by their physician or another health care provider. Colorectal cancer screening recommendations are now evolving rapidly in health care organizations. The evidence currently supports doing fecal occult blood testing every two years and periodic screening with flexible sigmoidoscopy. The optimal interval for sigmoidoscopic screening has yet to be determined, and various policy-setting organizations have recommended intervals ranging from two to ten years. Finally, death from cervical cancer in women aged 65 and older is rare (9.3 per 100,000) and even less common among women with normal Papanicolaou smears. Whereas Pap smear screening every one to two years is recommended for younger women, consideration can be given to discontinuing screening in older women with documented regular normal Pap smears.

Conclusions

We have attempted to provide concise and well-founded clinical recommendations that can promote healthy aging in older women, including the following specific actions:

- Assess risk factors for fracture and falls and modify those that can be changed. Ensure adequate intake of calcium and vitamin D.
- Engage women in a shared decision-making process about the use of hormone replacement for the long-term prevention of fractures and heart disease. Consider the risks and benefits, preferences, and health history of the individual woman being counseled.
- Monitor weight and discourage weight loss for most women. Evaluate changes in weight, either losses or gains, greater than 5% that occur over a 6- to 12-month period. Screen for vitamin B_{12} deficiency on a regular basis. Encourage the consumption of five or more fruits and vegetables each day, a diet low in total and saturated fat, and the use of a daily multivitamin.
- Encourage women to engage in enjoyable physical activities, especially walking and other low-intensity activities, for 30 minutes most days of the week.
- Encourage women to get regular screening for breast and colorectal cancer.

These interventions, if adopted consistently, have the potential to delay the onset or improve the course of many chronic conditions that are prevalent in later life. In so doing, these behaviors can decrease the period of disability older women experience in their last years and thus, have promise in making women's extended life expectancies a time of greater independence.

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SUCCESSFUL AGING

Optimal Medication Use in Elders

Key to Successful Aging

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Pharmacotherapy represents one of the most important ways in which the practice of geriatric medicine differs from conventional medical care. The older patient is a major consumer of prescription and nonprescription medications, and proper use of these agents can lead to more cost-effective strategies in reaching optimal health. A key difference in distinguishing appropriate from inappropriate drug use is evident in the themes of polymedicine and polypharmacy. Polymedicine describes the use of medications for an older population for the treatment of multiple co-morbid conditions, while polypharmacy represents a less-than-desirable state with duplicative medications, drug-to-drug interactions, and inadequate attention to pharmacokinetic and pharmacodynamic principles. The purpose of this paper is to outline strategies toward optimal medication use as a key to successful aging. Specifically, we discuss themes of cost-effective prescribing, the role of medication compliance, overuse and underuse of medication, over-the-counter products, alcohol abuse, and preventive medicine. In addition, we discuss policy implications and responsibility for ensuring the high quality of pharmaceutical care. The reader should have a practical understanding of the pertinent issues in geriatric clinical pharmacology and its relationship to successful aging.

(Monane M, Monane S, Semla T. Optimal medication use in elders: key to successful aging. In: Successful Aging. West J Med 1997; 167:233–237)

The beginning and end of each day for practitioners often feature prescribing a medication. Regardless of the various pathophysiologic mechanisms and the setting of care, the most common therapeutic intervention in medicine is the writing of a prescription.[1] This practice takes on even greater meaning in geriatric patients. Older people take about three times as many prescription medications as younger patients do, mainly because of the increased prevalence of chronic medical conditions. For this reason, multiple medications (polymedicine) may be beneficial in treating multiple illnesses.[2]

Ongoing advances in biomedical research have led to new and better prescription drugs, and today 24 million Americans aged 65 years or older receive prescriptions each year.[3] One study showed that elderly women took an average of 5.7 prescription drugs and 3.2 over-the-counter drugs concurrently.[4] These figures are noteworthy because the use of multiple medications increases the risk of adverse drug events and makes medication compliance more challenging.[5]

Pharmacotherapy as Cost-effective

Pharmacotherapy represents one of the most important ways in which the practice of geriatric medicine differs importantly from conventional medical care. Changes in both the pharmacokinetics and pharmacodynamics of drugs commonly used in the geriatric population have been described, and a discussion of them is beyond the scope of this article. Yet, the proper use of medications is perhaps the single most important medical strategy in the care of elderly patients. Optimal drug therapy is key to treating acute illness, maintaining current health, and preventing further decline, all three of which represent the paradigm of geriatric care and are prominent in the themes of successful aging.[6]

Medication Compliance

Definition of Compliance

Compliance can be defined as the extent to which a person's use of medications coincides with medical or

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health advice. Other investigators have chosen similar terms to describe this behavior, including adherence, fidelity, and maintenance, because compliance has been associated with negative connotations of servility or obedience.

Prevalence of Noncompliance

Various procedures have been used to evaluate compliance. Indirect methods include patient interview, physician estimate, pill count, and refill record. The first two approaches, patient interview and physician estimate, can detect 50% of cases of noncompliance quickly and inexpensively. In addition, these techniques offer the opportunity to provide immediate feedback, which also serves to show concern for a patient's well-being. The disadvantage of these techniques, however, is their dependence on a patient's memory and honesty and the skills of the interviewer. The pill count method, in which the number of tablets in a medication bottle is measured at two points over a given time interval, provides a more objective measure of the quantity taken. Nonetheless, this method is time-consuming and also assumes that all medications not in the container were actually consumed. The refill-record method uses a standardized measure from pharmacy data or large fiscal databases of filled prescriptions to examine the continuity of medication use and gaps in therapy, but this method requires that all prescriptions be reimbursed through the same administrative source. More direct methods of assessing compliance include blood level monitoring and urine assays to measure drug metabolites or marker compounds. Although both these direct measures provide objective data that are valid and quantitative, their use is limited by their expense, inconvenience, and unavailability for some drugs.[7]

Although compliance with short-term medication use has been reported to approximate 80%, the same cannot be said for long-term medication use: several studies of elderly persons with common and serious clinical disorders such as congestive heart failure, diabetes mellitus, and tuberculosis have found compliance rates between 40% and 60% for long-term therapy.[8] Another classification of compliance represents medication use patterns along a continuum. Half to two thirds of patients use medication satisfactorily (≥80% of prescribed doses). Another third of patients are partially compliant, taking 40% to 80% of prescribed doses; the rest take their drugs erratically, possibly undercutting even the best-conceived regimens.

Poor compliance with prescribed medications can have major clinical consequences, especially in older persons. If the existence of noncompliance is not recognized, the physician may increase the dose of the initial medication or add a second agent, increasing both the risk and the cost of treatment.

Strategies to Improve Compliance

What strategies can be used to improve compliance? Approaches that have been shown to be effective in the past include educating patients, promoting compliance, and simplifying the medication regimen. Successful compliance, however, depends on the actions by not only the physician and patient but also the support system (for example, caregiver) of the patient. Given the rapid increase in diagnosis and therapeutic options, obtaining the utmost benefit of medication use will play a major role in the coming decade in improving the quality of patient outcomes.

Polypharmacy

Definition

Polypharmacy or polymedicine has many definitions. Healthy People 2000 defined polypharmacy as the concurrent use of multiple prescription drugs and over-the-counter medications and considered it the principal drug safety problem in the United States.[9(p67)] Other definitions have included a measure of appropriateness such as the prescription, administration, or use of more medications than are clinically indicated, or when a medical regimen includes at least one unnecessary medicine. The use of one medication to treat the adverse effects of another medication represents polypharmacy as well; there are exceptions to this rule, however, such as potassium supplementation for diuretic therapy. On the other hand, a case of osteoarthritis in an elderly woman who is being treated with acetaminophen with codeine in which the patient requires three laxatives to relieve the codeine-induced constipation is an example of an adverse consequence of polypharmacy. Finally, some researchers have quantified the definition: the concomitant use of five or more medications, for instance. This definition is useful as a quick screen to identify patients whose medications may need to be reviewed—that is, there is a high probability of inappropriate prescribing. When using a definition that includes some measure of appropriateness, remember that it takes only one medication to cause a problem.

Frequency of Polypharmacy

In one study, explicit criteria were developed to measure the frequency with which elderly nursing home residents were exposed to medication use considered inappropriate, for an inappropriate duration, or in a dose exceeding criteria limits.[10] Of the residents, 40% had at least one inappropriate medication order and 10% two or more orders. In another study, these same criteria were applied to respondents aged 65 and older to the 1987 National Medical Expenditure Survey as a means of measuring inappropriate prescribing for community-dwelling elderly persons.[11] Based on this sample, the investigators concluded that 6 million older Americans (almost 25% of the population) were exposed to possibly inappropriate medication use.

Origins

Polypharmacy has many origins. The use of several prescribers or several pharmacies has been shown to

increase the risk for medication-related problems. These two origins are both somewhat within a patient's or informal caregiver's control. For example, many patients will assume that all their prescribers communicate with each other and therefore are aware of what each is prescribing or recommending. Patients may also incorrectly assume that the computer databases of different pharmacies are linked and will identify potential drug-drug interactions. As a means of prevention, patients should provide each prescriber and pharmacist with a list of all their medications: prescription, over-the-counter, and alternative therapies. Patients should also be encouraged to use only one pharmacy or one chain whose database is linked or to join a prescription drug plan that links a network of participating pharmacies. Physicians and pharmacists should also provide patients with a regular, comprehensive medication review to eliminate unnecessary medications, identify possible medication-related problems, and answer patients' questions about their medication regimen.

Polypharmacy also has an origin in patients' belief that they need a pill for every ill. It is incumbent that prescribers not use writing an unnecessary prescription as a means of ending an office visit or satisfying a patient's demands. The lack of a health-educated patient population may be another cause of polypharmacy. A patient's lack of knowledge of what is caused by normal aging versus disease may lead to unnecessary medication use. For example, insomnia in an older adult may be due to the normal sleep changes of aging. Explaining these changes and reviewing sleep hygiene may be sufficient treatment. Before patients can receive appropriate education, physicians, pharmacists, nurses, and other health professionals must have the necessary knowledge and understanding of these principles.

Consequences of Polypharmacy

The consequences of polypharmacy are multiple and include adverse drug events, drug-drug interactions, the duplication of therapy, decreased quality of life, and unnecessary financial costs. The use of multiple drugs is a risk factor for adverse drug events. Between 10% and 17% of hospital admissions for older patients are related to an adverse drug reaction.[12] Another study attributed 73% of adverse drug reactions to unnecessary drugs, possible drug interactions, or contraindicated medications.[13]

The risk of drug-drug interactions increases with the number of medications taken. Data from the Swedish National Formulary identified at least one possible drug interaction in 31% of mostly older outpatients. Patients with at least one drug interaction used substantially more medications than those without (mean, 8.1 versus 5.2.).[14] The use of several physician-prescribers was the single most important factor associated with possible drug-drug interactions among persons aged 70 years and older in Quebec.[15] The use of a single pharmacy reduced the risk of a possible drug-drug interaction by 21% to 32% for all drugs.[15]

Patients' quality of life can also be adversely affected by polypharmacy. Prescription drug use was associated with a decreased ability to perform activities of daily living and an increase in symptoms in 60% of women aged 65 years and older in Baltimore, Maryland.[16] Another study found that the risk of an adverse drug reaction manifesting as cognitive impairment was increased more than ninefold for those taking four or more medications.[17] In a study that assessed the relationship between medication and incontinence in 128 patients enrolled in a study of incontinence, 62% of patients were receiving one or more medications that had possible urologic effects.[18]

Undermedication or Omission

The frequency and consequences of undermedication or omission have not been as extensively studied as multiple medication use. The limited data available suggest that a substantial number of older persons who might benefit from drug therapy are not taking the appropriate medications. Among participants in the Established Populations for the Epidemiologic Studies of the Elderly (EPESE), between 10% and 29% who reported their health as fair or poor also reported that they were taking no prescription medications.[19]

In one study, 49% of patients at discharge and in outpatient follow-up had one or more dosage problems as judged by a seven-member physician-pharmacist panel.[20] Inadequate dosage was identified in 21% of patients, with calcium supplements, transdermal nitroglycerin, and bronchodilators the most frequently underdosed medications. In addition, 55% of patients had one or more necessary medications omitted from their profile. Iron supplements for postoperative patients, cholesterol-lowering agents, oral hypoglycemic agents, and bronchodilators were the most frequent omissions.

Over-the-Counter Medications

Simply defined, over-the-counter medications are those medications that are obtained without a prescription. The fact that patients and physicians alike often think that these nonprescription drugs have little pharmacologic activity and are relatively safe and easy to use is troublesome for optimal medication use. Although nonprescription medications represent an important part of the therapeutic package available to patients and physicians, physicians should be aware of their patients' use of these drugs under all circumstances and also of the benefits and risks of these medications.

The history of nonprescription drugs in the United States can be traced back to the 1850s, when most health care was provided not by physicians but by lay practitioners. Two powerful trends, patient empowerment and the reclassification of many prescription medications to over-the-counter status, are important influences that have led to increased over-the-counter drug use. A sur-

vey has confirmed that the use of nonprescription drugs was not due to substituting for prescription medications or for obtaining professional medical care for illnesses perceived as serious by the patient.[21] Patients with higher education levels, elderly patients, those with less time available for physician visits, and those with less access to professional medical care are more likely to use nonprescription medications, as are patients who are socially isolated or who have chronic illnesses. Interestingly, the use of nonprescription and prescription drugs is correlated particularly because less healthy persons use more of both types of these drugs.[21]

Alcohol and Medications

The consumption of alcoholic beverages by older persons is not uncommon, yet consumption in combination with medications is potentially dangerous. Interactions between alcohol and many medications frequently taken by the elderly are well described. For example, alcohol consumption in combination with other medications known to cause drowsiness can potentiate the sedation and impair physical and cognitive function, and its use with nonsteroidal anti-inflammatory agents can increase the risk for gastrointestinal bleeding. Alcohol can potentiate the blood pressure–lowering effects of antihypertensive and diuretic agents; increase the hepatic metabolism of warfarin sodium and phenytoin, thereby minimizing their therapeutic activity; and reduce the absorption of vitamins. In addition, alcohol use may worsen symptoms or accelerate the progression of chronic disease states common in elderly persons, such as depression, congestive heart failure, and diabetes mellitus. A periodic review of medication use should include screening questions on alcohol use as well.

Preventive Medicines

Medications play a large role in preventing disease in older adults. The benefits of aspirin use in the prevention of myocardial infarction and stroke are well documented. It is clear that the control of systolic and diastolic blood pressures reduces both the morbidity due to stroke, coronary heart disease, and congestive heart failure and all-cause mortality. The treatment of hyperlipidemia in older patients remains controversial; yet, population-based surveys of persons aged 65 and older indicated that less than 0.5% of respondents were receiving lipid-lowering medication.[22,23] Postmenopausal estrogen replacement decreases the risk for osteoporosis and heart disease and may have a role in preventing memory loss or Alzheimer's disease. Estrogen therapy has not been widely prescribed for nor accepted by older women, however.[24] The use of β-blockers after acute myocardial infarction has been reported to be less than 25%.[25] Warfarin is the recommended anticoagulation agent for atrial fibrillation, but it is not widely used because of the fear of bleeding complications.[26] Much work is needed to increase the role of prevention in elderly patients and should be directed to physicians and patients alike.

Policy Implications

Public Versus Private

Many vehicles are currently available for improving medication use. Several strategies focus on computer-assisted reminders to alert either a prescriber or pharmacist of the dangers associated with either a single medication or multiple drug-drug interactions in patients. Yet, these systems are limited by the accurate reporting of the medication use and the completeness of the data on medication use patterns. A surveillance system to track medication use across several pharmacies is needed: such a system exists for a variety of fiscal-claims databases, and this is one advantage of the prescription drug plans offered by pharmaceutical benefit managers. Further integration of the health care system will lead to more coordinated care and improve prescribing in this vulnerable population.

Who Is Responsible?

The responsibility for ensuring high-quality care around pharmaceutical use remains a challenge. Prescribers like to think that they are prescribing in the best interests of their patients, yet they are left with incomplete information in making this link. Because there is no "diagnosis-related group" or International Classification of Diseases codes for medication use, large population studies become difficult. The perverse fiscal system in which Medicare pays for therapeutic failure (noncompliance) or adverse drug effects (polypharmacy), but does little to either pay for or supervise drug use in the ambulatory care environment furthers uncoordinated care. The new wave of capitated agreements in which physicians are at risk for both the cost of the prescription therapy and that associated with adverse drug events has the potential to improve drug use overall.

Summary Points

- The use of any medication puts a person at risk for an adverse drug event. Because of changes in pharmacokinetics and pharmacodynamics and the prevalence of chronic disease, this is especially true in elderly persons.
- The omission or underdosage of a medication(s) may result in an incomplete therapeutic response or progression of a disease state. Physicians should balance both benefit and risk to optimize their prescribing practice.
- The balance of too few, too little, too many, and too much is delicate with respect to medication use by older patients, and thus, any medication regimen must be tailored to an individual patient's needs.

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SUCCESSFUL AGING

Successful Aging Calls for More Than Drugs

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(Ershler WB, Gravenstein S. Successful aging calls for more than drugs. In: Successful Aging. West J Med 1997; 167:238–239)

There is an old story of a famed Boston cardiologist making visiting rounds on the wards of a major midwestern university. Outside of the patient's room, a large team of physicians, nurses, and students listened to the medical intern present the complex history of an elderly patient with congestive heart failure and a variety of other chronic medical illnesses, some or all of which contributed to her debilitated state and current hospital admission. The intern had carefully prepared his presentation and detailed a robust medical history, together with a verbatim recitation of her 16 medications including dose and schedule. The entourage proceeded into the patient's room for a brief visit and examination, and the professor exchanged pleasantries with the patient, primarily about fishing in the Canadian boundary waters. On exiting the room, the group waited for the eminent scholar to wax eloquent on any of the many issues that the patient presented. Instead, he simply declared that it was obvious that this patient would receive the greatest benefit if her medication list was cut to three drugs. He then began walking in the direction of the next room, and the bewildered group followed, no one confident enough to pursue the question. Finally, a third-year student, perhaps because of his most junior status or his own sense of inquisitiveness, asked the question, "Which three?" Thereupon, the scholarly professor mumbled "any three."

In this volume of THE WESTERN JOURNAL OF MEDICINE, Monane and colleagues have concisely reviewed the data that support what the professor knew, that medication use among older people contributes to the phenotype of frailty. Drugs are overprescribed, nonprescription drugs are overused, and it seems no one is keeping score. Furthermore, as they point out, assuring good medical care and, indeed, overall well-being for older patients requires rigorous attention to the details of adverse drug effects, drug-drug interactions, compliance, and the influence of nutrition and alcohol on the various pharmacologic indices.

Yet, it is difficult to concede, as the authors suggest in the title of their manuscript, that optimizing medication use is a "key to successful aging." First of all, there is an important distinction between aging and disease. Whereas clinicians think of aging most commonly when considering older people, aging is not a disease but a continuum of normal or at least predictable functional alterations that occur over time. These functional alterations, some of which are the result of defined, age-associated cellular and subcellular changes, do not generally cause symptoms and should not be thought of as disease. Thus, with the exception of those who are tempted to take fashionable compounds such as dehydroepiandrosterone (DHEA) or melatonin for their purported but unsubstantiated antiaging effects, prescriptions are not written and over-the-counter drugs are not taken for aging per se.

A useful way to think about aging is that it is associated with a diminished capacity to maintain homeostasis. Thus, exogenous insults well tolerated in youth may be lethal in old age. In the absence of these exogenous factors, however, there is sufficient functional reserve in each of our organ systems to survive 120 years, or possibly more.

Medications and their complications do not fit neatly in this model. Certainly drugs taken to cure a disease put patients back on track and allow successful aging. Drugs taken for chronic disease may ameliorate symptoms and improve quality of life, a tenet of successful aging. But adverse reactions and drug-drug interactions can influence quality of life in the opposite direction. It is important to remember that drugs are prescribed to treat disease and that aging is not a disease. Thus, assuring the best medication use is, in effect, modulating one of those exogenous factors that might otherwise distort the normal aging trajectory during a period of diminished homeostasis (advanced age).

Getting the optimal benefit of medication use, however, is only one of a number of such interventions that sim-

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ilarly would promote successful aging and is only one of the modalities in geriatricians' repertoire. Much of the functional decline common in older people and within geriatricians' purview requires skills that are still not widely taught in our medical schools or residency programs. For example, successful aging, when defined as maintaining independence, may require a practitioner who knows how and is willing to mobilize a variety of community resources, such as social work, physical and occupational therapy, pharmacy, and clergy. Geriatricians are a component of a team, and geriatricians' success might be measured by how well they function within the team.

The anecdote of the "eminent scholar" and the 16 medications is analogous to the situation of an older woman in an emergency department with a hip fracture. To an orthopedic surgeon, the key to her successful aging might be optimal fracture repair, just as evaluating a long and complex list of medications is for a traditionally trained and highly competent internist. No doubt, both are critical, but both are not enough. Here is where the geriatrics perspective comes in. Each patient would benefit from an interdisciplinary approach focused on the balance of medical care for acute and chronic illness, crisis prevention, health promotion, and social, economic, and psychological needs. The success of such an approach could be measured as quality of life and maintenance of independence, both of which are surrogates of "successful aging."

SUCCESSFUL AGING

Heart Health in Older Adults

Import of Heart Disease and Opportunities for Maintaining Cardiac Health

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Coronary heart disease remains the leading cause of morbidity and mortality in older adults, despite improved survival and declining mortality. This article describes the prevalence and impact of heart disease on people's lives, singly and in combination with other diseases. It then reviews current findings as to the risk factors for CHD in older adults and the underlying physiologic changes of aging plus pathophysiologic changes of hypertension and CHD in impairing the ability of older adults to respond to exercise and other stressors, and the effects of exercise training in attenuating the adverse cardiovascular changes of aging. This information provides a basis for considering opportunities for prevention of heart disease and maximizing heart function. The article concludes by describing the known contribution of preventive measures to declines in heart disease in older adults.

(Fried LP, McNamara RL, Burke GL, Siscovick DS. Heart health in older adults: import of heart disease and opportunities for maintaining cardiac health. In: Successful Aging. West J Med 1997; 167:240–246)

Coronary heart disease remains the leading cause of morbidity and mortality in older adults, even though survival has improved[1,2] and its incidence in the United States has declined over the past few decades.[3,4] The acute death rate from coronary disease has decreased substantially more than the chronic death rate (4.0% annually versus 2.5%),[3,5,6] leading to conclusions that survival rates in patients with heart disease are improving. Consistent with this, prevalence rates are rising among older adults, resulting in an increase in the absolute number of older adults with coronary heart disease.[3,7] More older adults are living—and living longer—with chronic heart disease. We will examine here the prevalence of and risk factors for cardiovascular disease in older adults, the physiology of aging and the effects of exercise, so as to consider opportunities for maintaining cardiovascular health.

The import of coronary heart disease in older adults is reflected, in part, by the prevalence rates. In the Cardiovascular Health Study (CHS), a population-based study of 5,201 men and women aged 65 years and older in four US communities,[8] the prevalence of heart disease increased with age (5-year age groups, from 65 to 69 to 85 and older) and varied by sex. Myocardial infarction (MI) was found in 11% to 18% of men and 4% to 9% of women older than 65, varying with age group; angina pectoris was found in 15% to 17% of men and in 8% to 13% of women; and congestive heart failure was present in 1% to 3% of both men and women between 65 and 84 years.[9] Prevalences of MI and congestive heart failure were higher in black men and women than in whites, whereas the rates for angina pectoris were slightly lower.[10] In addition, the prevalence of unreported, and possibly silent, MIs was high; 23% of men and 38% of women 65 and older with electrocardiographic evidence of old MI did not have a known history of infarction.[9] In the same population, 13% of men and 9% of women had ischemic episodes on 24-hour ambulatory electrocardiograms, including 9.6% of participants without any history of MI and no major or minor resting electrocardiographic abnormalities.[11] Overall, 28.9% of men and 19.3% of women 65 and older had heart disease.[12] In comparison, the Women's Health and Aging Study, which evaluated the third most

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ABBREVIATIONS USED IN TEXT

A-$\dot{V}O_2$ = arteriovenous oxygen
CHS = Cardiovascular Health Study
MI = myocardial infarction
$\dot{V}O_2$max = maximum oxygen consumption

disabled women aged 65 years and older living in the community, 20.9% reported a history of MI, 20.8% a history of angina pectoris, and 8.3% a history of congestive heart failure.[13]

Subclinical cardiovascular disease is also prevalent in older adults. A summary index of subclinical disease was created in the CHS, based on measurements of several vascular beds using electrocardiographic and echocardiographic abnormalities and common carotid artery wall thicknesses as measured by ultrasonography, ankle-brachial blood pressure, and positive response to the Rose Questionnaire for angina. Using this index, 36.1% of women and 38.7% of men in the CHS had subclinical disease only. The prevalence of subclinical disease increased with age, so that only 12.6% of those aged 85 years and older had neither clinical nor subclinical cardiovascular disease.[14]

The import of coronary heart disease in older adults is also expressed by its effects on individual patients. Heart disease is among the major causes of disability that we associate with aging, whether evaluated by aggregate associations or through individuals. Regarding the latter, participants in the CHS cited heart disease, along with lung disease, as the most frequent cause of difficulty in tasks requiring the ability to perform physical work or exercise tolerance, such as walking half a mile, doing heavy housework, walking up ten steps, and lifting or carrying 4.5 kg (10 lb).[12] Shortness of breath was the symptom most associated with difficulty in these same tasks. In analytic approaches used to understand the association of heart disease with function, angina pectoris has been shown in the Framingham Study to be predictive of disability; angina pectoris was more predictive than MI or coronary artery insufficiency.[15] In the CHS, cross-sectional analysis showed that angina pectoris requiring nitroglycerin use, MI, congestive heart failure, shortness of breath, and left ventricular systolic dysfunction by echocardiography were each independently associated with difficulty in performing the tasks of daily life, ranging from mobility and exercise tolerance–demanding tasks to basic self-care tasks.[16] In addition, there is early evidence from the CHS cohort that subclinical cardiac functional impairments, as measured by echocardiography, may be associated with disability as well (L.P.F., D.S.S., J. M. Gardin, H. S. Klopfenstein, J. A. Robbins, and P. J. Savage for the Cardiovascular Health Study Group: "Association of Subclinical Cardiac Impairments With Physical Disability in Older Adults," (1997). These data all indicate that heart disease has substantial effects on the well-being and independence of older adults. A summary expression of this has been provided by Kosorok and associates, who estimated that 4 of the 31 restricted-activity days per person per year reported by older adults were due to heart disease.[17] Another calculation, of population attributable risk, indicates that 9% of disability and dependency in older adults is caused by heart disease.[18] Given this perspective, the results of the effective prevention and treatment of cardiac disease will include preventing the disability and loss of independence associated with aging.

Heart disease also interacts with other diseases in causing adverse consequences. This has been best studied in terms of the synergistic effects of heart disease and arthritis. In a study by Ettinger and colleagues, those with heart disease but no arthritis had a 2.3-fold increased risk of having difficulty in ambulation over those with neither disease. When arthritis was also present, the relative risk for both heart disease and knee osteoarthritis was 13.6.[19] Clinical observation suggests that a good proportion of this interaction may lie in the decreased efficiency of ambulation and increased energy demands and stress on the heart in the presence of arthritis of the lower extremities.[20] Heart disease and arthritis commonly coexist, and particularly so in disabled persons. For example, in the Women's Health and Aging Study's population of moderately to severely disabled older women, 10% reported both heart disease and arthritis (L.P.F., K. Bandeen-Roche, J. D. Kasper, and J. M. Guralnik: "Association of Comorbidity With Disability in Older Women: The Women's Health and Aging Study," 1997). Overall, 50% of older adults have two or more chronic diseases. The joint effects of heart disease with other diseases need to be considered in treatment goals, as do the secondary effects of medications for heart disease on other conditions.

Thus, both clinical and subclinical cardiac diseases are prevalent in older adults. Changing rates, as described earlier, suggest that these rates can be modified.

Risk Factors for Cardiovascular Disease

Factors associated with the incidence of MI in adults older than 65 years also were assessed in the CHS.[21] Over about a five-year follow-up period, incidence rates of MI were higher in older participants and in men (21 per 1,000 person-years) than in women (7 per 1,000 person-years).[22] Predictors of incident MI included elevated systolic blood pressure, cigarette smoking, and elevated serum glucose levels. Of interest, in this cohort of older adults, serum lipid or lipoprotein measurements were not significant predictors of incident MI. A number of measures of subclinical disease, including the intimalmedial thickness of the internal carotid artery, decreased cardiac ejection fraction, and a low ankle-arm index, were significant predictors of incident MI after adjustment for age and sex. Based on these results, modifiable risk factors such as blood pressure, smoking, and serum glucose levels are associated with an increased risk of MI, and interventions on these factors may facilitate the primary prevention of this disease in older adults.

A number of risk factors are shared between incident MI and stroke in older adults. Factors associated with incident stroke rates in older adults over about a three- to four-year follow-up period were assessed in the CHS cohort.[23] The stroke incidence was similar in men and women and increased with age.[24] Incident stroke in these older adults was associated with diabetes mellitus, elevated systolic blood pressure, increased left ventricular mass or wall motion abnormalities, carotid artery stenosis, and atrial fibrillation. Of interest, aspirin users free of coronary heart disease, atrial fibrillation, transient ischemic attacks, or claudication at rest had a 52% increase in stroke incidence even after adjustment for other risk factors. The stroke incidence also was associated with elevated levels of modifiable risk factors and with subclinical disease measures. Perhaps more important is the fact that interventions that reduce the burden of incident MI in older adults—elevated systolic blood pressure, possibly glycemic status, and the like—would also be expected to favorably affect stroke incidence rates.

In this study, prevalent subclinical cardiovascular disease was associated with a number of risk factors also associated with clinical disease: age, systolic blood pressure, fasting glucose levels, high blood pressure, and smoking in both women and men, and, in addition in women, diastolic blood pressure, low-density lipoprotein–cholesterol levels, high-density lipoprotein–cholesterol levels, and leukocyte count. In addition, isolated systolic hypertension was associated with subclinical cardiac diastolic function and increased intimalmedial thickness of the carotid artery.[25]

In particular, carotid artery ultrasonography has been used to noninvasively assess factors associated with atherosclerosis in numerous population-based studies.[26,27] In the Atherosclerosis Risk in Communities (ARIC) study of middle-aged adults, a number of factors were associated with increased carotid artery wall thickness, including age, hypertension, active and passive cigarette smoking, serum lipid or lipoprotein levels, diabetes mellitus, dietary antioxidant and fat intake, and hemostatic factors.[28–36] In the CHS study of older adults, factors associated with atherosclerosis include cigarette smoking, ankle-arm index, hormone replacement therapy (women), hemostatic factors, diabetes mellitus and glucose intolerance, hypertension, and left ventricular hypertrophy.[37–41] These data document the importance of behavioral and clinical factors on the burden of atherosclerosis in middle-aged and older adults.

Several recent reports highlight the opportunities for maintaining cardiac health and the effectiveness of prevention and treatment. First, in the CHS, the presence of subclinical cardiovascular disease identified older adults who are at high risk of progressing to clinical disease.[42] Overall, over a three-year follow-up period, those with subclinical disease had a twofold higher risk of coronary heart disease and mortality than those without subclinical disease. In women, 43% of incident coronary heart disease was due to subclinical disease; in men, the proportion was 37%. These data suggest that the primary prevention of subclinical cardiovascular disease is likely to have a substantial impact on rates of clinical disease. Given, however, that in CHS, almost half of older adults had subclinical disease at the baseline evaluation, effective secondary prevention of clinical cardiovascular disease is also critical. This is accomplished through targeting those with subclinical disease for interventions to minimize factors that precipitate transitions to clinical disease.

Cardiovascular Changes With Aging

Clear differences exist in the cardiovascular systems of young and older people. How much these differences can be attributed to the pathophysiologic effects of disease and how much to the physiologic effects of aging are less clear. The increased prevalence of disease with age, particularly coronary artery disease and hypertension, complicates the distinction. Changes in the heart and vasculature associated with aging, however, may interact with the effects of superimposed disease, possibly altering the effectiveness of therapy. Prevention and the treatment of disease have contributed substantially to the decreasing rate of cardiovascular mortality over the past three decades.[3] In addition, delays in the physiologic effects of aging may also have contributed. We summarize some relevant concepts derived from studies that sought to isolate the physiologic effects of aging from the pathologic effects of disease, background information essential to maximizing prevention and therapy.

Arterial vessel walls undergo major structural changes with age, including increased collagen deposition and hypertrophy of the smooth muscle cells, that in turn lead to decreased vascular elasticity.[43,44] These structural changes are compounded by a decrease in β-adrenergic receptor reactivity,[45,46] leading to a decreased capacity for vasodilatation. The resultant increase in systolic blood pressure, and thus afterload, with age has been repeatedly shown.[46–49] Less known, but potentially as detrimental, is an increase in the pulse-wave velocity.[47,48] In normal physiology, a pressure wave is referred from the aorta back to the heart during diastole, aiding coronary perfusion. The age-associated increase in pulse-wave velocity produces the referred pressure wave during systole, further increasing afterload.

Together, the increases in systolic pressure and pulse-wave velocity contribute to the age-associated structural and functional changes in the myocardium, which primarily affect diastolic function. The increased afterload causes connective tissue deposition and increased myocyte size,[43,50] which leads to left ventricular wall thickening[51,52] and decreased left ventricular compliance. Decreased β-adrenergic activity in the myocardium also impairs relaxation.[45,46] As a result, diastolic filling abnormalities can be seen on echocardiography. The peak velocity of the rapid early diastolic filling (the "E" wave on M-mode echocardiography) decreases, and the late component (the "A" wave) increases.[53]

Systolic function is less affected by the aging process. The resting ejection fraction does not appear to

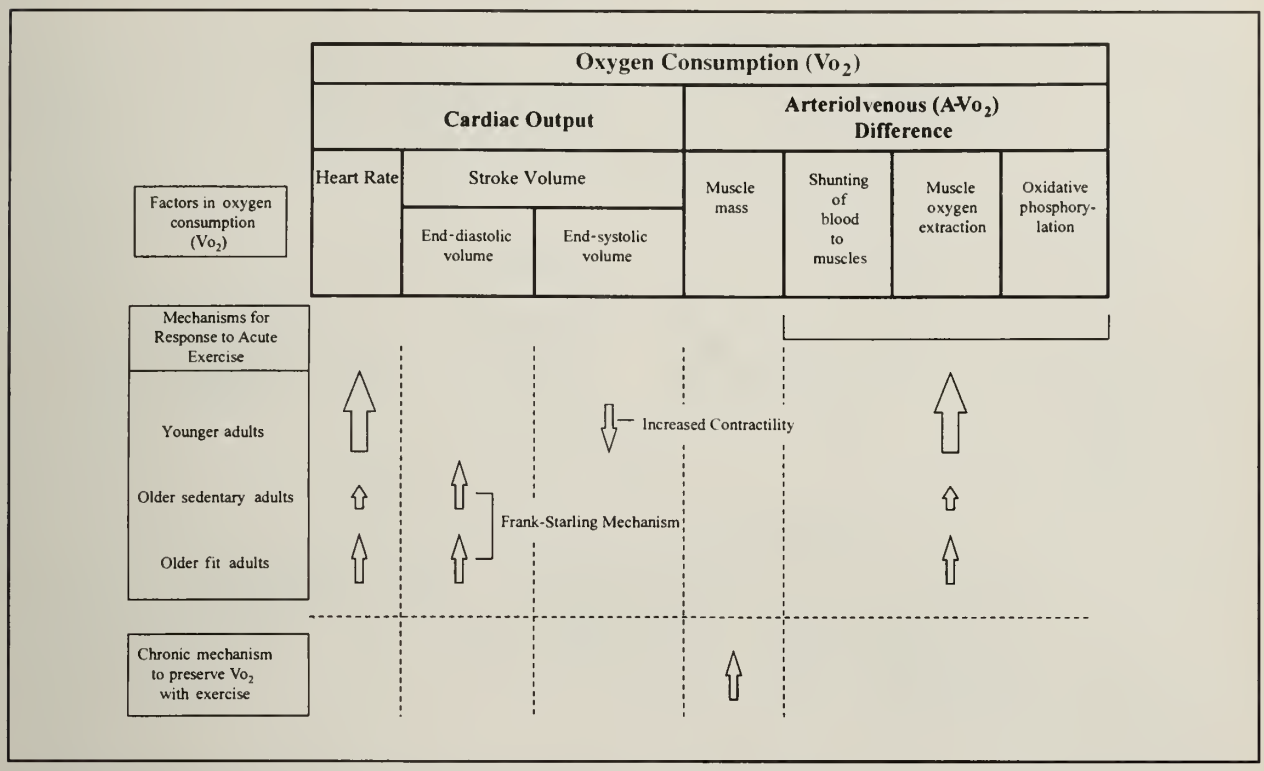

Figure 1.—Physiologic factors that make up oxygen consumption are shown. Different age and fitness groups respond to exercise by relative magnitudes of mechanisms (as shown by the different-sized arrows), and an important long-term mechanism can preserve maximum oxygen consumption.

change with age.[49,54–56] The resting heart rate and cardiac output remain relatively constant because of an increase in the level of catecholamines[45] to offset the decreased β-adrenergic receptor activity. Overall, the resting heart adapts well to the structural and functional changes associated with aging.

Effect of Exercise on the Physiology of Aging

Age-associated changes in the cardiovascular system, however, become more apparent during exercise. Most notably, the maximum oxygen consumption ($\dot{V}O_2max$) with exercise decreases substantially. Both components of the $\dot{V}O_2max$, cardiac output and arteriovenous oxygen ($A\text{-}\dot{V}O_2$) difference, are affected (Figure 1). In normal, younger hearts, cardiac output during exercise is primarily augmented by increasing heart rate and increasing oxygen extraction, with some increase in contractility (decreased end-systolic volume). In older adults, the maximum heart rate achieved with exercise is substantially attenuated.[45,46,49,56,57]

An overall exercise-induced increase in the stroke volume, the other component of cardiac output, appears to be preserved with aging.[46,54,56] Older hearts, however, increase their stroke volume using a different physiology than younger hearts. Younger adults, particularly men, rely on increasing contractility, producing a decreased end-systolic volume. Older adults instead increase their end-diastolic volume through the Frank-Starling mechanism to increase cardiac output during exercise.[46,54,56] Interestingly, younger women may also rely more on the Frank-Starling mechanism than do younger men,[55,58] though conflicting findings have been reported.[59] More research is needed to define gender differences in the physiology of aging.

The $\dot{V}O_2max$ depends not only on cardiac output but on the $A\text{-}\dot{V}O_2$ difference. The $A\text{-}\dot{V}O_2$ difference increases with exercise in all ages, but less so in older adults.[45] Decreased muscle mass in older adults, compared with younger adults, explains part of this attenuation of oxygen consumption. The abilities to shunt blood to muscle and of the muscle to extract the oxygen and the rate of oxygen phosphorylation are other mechanisms that younger adults use to increase oxygen consumption with exercise that are attenuated in older adults.[45,59,60]

In summary, changes associated with aging primarily affect arterial elasticity, ventricular compliance, and β-adrenergic receptor activity. Although these changes are well tolerated at rest, in the presence of stressors on the heart, such as exercise, older adults have an impaired ability to increase heart rate and contractility, leading to a reliance on the Frank-Starling mechanism to augment cardiac output. Oxygen extraction is also attenuated in older adults, primarily through decreased muscle mass. Superimposed on these physiologic changes of aging, diseases such as hypertension and coronary artery dis-

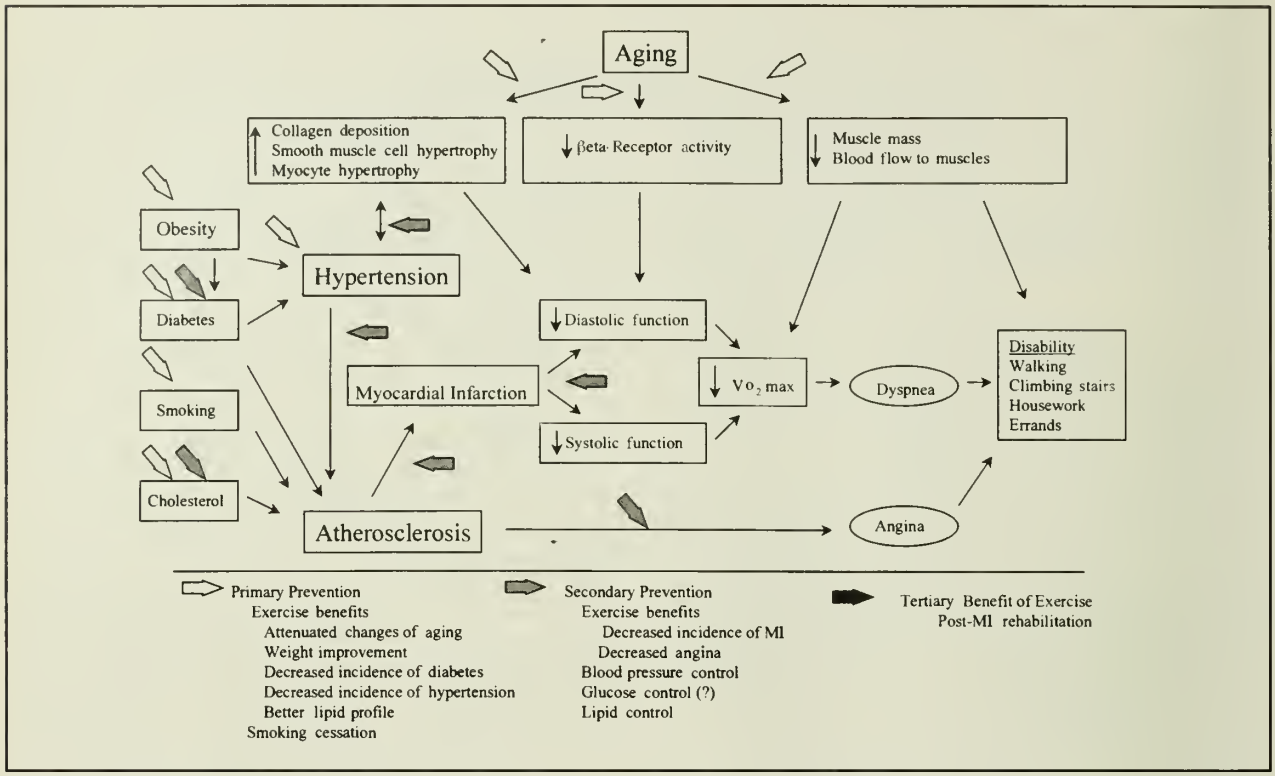

Figure 2.—The schematic shows age and disease effects on the development of disability and possible target areas for intervention. The thick arrows in the diagram correspond to the levels of prevention listed below the diagram. MI = myocardial infarction, VO_2max = maximum oxygen consumption

ease further impair the ability of older adults to respond to exercise and other stressors.

Effects of Exercise Training

As discussed earlier, clear differences in the way older adults respond to exercise can be identified. Is prevention possible? An exercise training program can attenuate some of the adverse changes in the cardiovascular system with aging (Figure 1). In one study, a decline with age in the $\dot{V}O_2$max was 50% greater in sedentary men and women than in their exercise-trained counterparts.[57] Exercise training was defined as 30 minutes of strenuous exercise three to four times a week for several years. In fact, the $\dot{V}O_2$max was higher in exercise-trained elderly men and women than in sedentary men and women 30 to 40 years younger. Age-related effects on maximum heart rate and oxygen extraction were attenuated in the trained subjects. In another study, exercise training was shown to improve the $\dot{V}O_2$max by peripheral adaptations without increasing end-diastolic volumes or contractility.[60]

In addition to increasing exercise capacity directly, exercise training has been shown to affect positively many age-related changes in cardiovascular risk factors and physiology at rest, including body fat, blood pressure, cholesterol level, and muscle mass.[61] The sedentary lifestyle that many older adults have, whether they are community-dwelling or residing in assisted-living facilities, may exacerbate losses of muscle function. A high-intensity strength program, even in institutionalized people, has been shown to result in increased strength and functional performance.[62]

Opportunities for Maximizing Cardiac Health

Cardiovascular disease remains the leading cause of morbidity and mortality in older adults. The prevalence of heart disease, both clinical and subclinical, increases with age. Serious comorbid diseases in older adults interact with heart disease to cause greater morbidity and mortality. The physiologic effects of aging occur in conjunction with the adverse effects of disease on the cardiovascular system and in combination may lead to disability in older adults (Figure 2). Modifying risk factors such as stopping smoking, controlling blood pressure,[63,64] and managing glucose levels are keystones of prevention. The benefits of lipid management in older adults remain controversial.[65,66] Exercise training appears clearly beneficial in augmenting primary and secondary prevention, including directly decreasing the incidence of MI[67,68] and lessening anginal symptoms.[69] Exercise is also an indispensable component of post-MI rehabilitation.[69,70]

In the absence of incapacitating cardiovascular disease, dementia, or gait disturbances, recommendations

for exercise in older adults are not substantially different from those for younger people,[71] including 5 to 10 minutes of warm-up, 20 to 40 minutes of aerobic exercise at 60% to 85% maximum heart rate, and 5 to 10 minutes of cool down, three to five days per week. Starting slowly and progressing gradually permit an appropriate exercise program.

Both primary and secondary prevention of coronary heart disease appear to be effective on a population basis. Hunink and co-workers recently reported that for the period 1980 to 1990, primary prevention explained 25% of the decline in the mortality of coronary heart disease through a decrease in its incidence.[3] Moreover, 29% of the decline was explained by a secondary reduction in risk factors in patients with coronary artery disease and 43% by other improvements in the treatment of patients with coronary heart disease. These findings indicate both success to date from clinical approaches to prevention and treatment and optimism for the future in maintaining cardiovascular health. Approaches designed specifically for older adults should yield even higher rates of improvement. Thus, primary and secondary prevention through risk factor modification and exercise are keys to successful cardiovascular aging.

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SUCCESSFUL AGING

Hear Ye? Hear Ye! Successful Auditory Aging

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Age-related hearing loss (presbycusis) is a multifactorial process that affects nearly all people in their senior years. Most cases are due to a loss of cochlear hair cell function and are well mediated by communication courtesy and modern amplification technology. Severe hearing loss is generally due to cochlear problems or age-related diseases and may require speech reading, assistive listening devices, and cochlear implants, depending on the degree of loss. Presbycusis may seriously impair communication and contribute to isolation, depression, and possibly dementia. Accurate diagnosis and prompt remediation are widely available but are frequently underused. Geriatric health care and well-being is enhanced by the detection and remediation of communication disorders.

(Gates GA, Rees TS. Hear ye? Hear ye! Successful auditory aging. In: Successful Aging. West J Med 1997; 167:247–252)

Hearing loss is a frequent problem in the senior years of life, but the magnitude of the hearing loss varies widely. Some older persons have minimal, nonconsequential hearing impairment, and others become isolated from friends and family because of their hearing. Hearing loss impairs communication, subtly at first and increasing with the magnitude of the loss. Hearing impairment contributes to social isolation, depression, and loss of self-esteem and has been implicated as a cofactor in senile dementia.[1]

Presbycusis—literally, elder hearing—is the general term applied to age-related hearing loss and is used to signify the sum of all the processes that affect hearing with the passage of time. The aging process has three distinct components: intrinsic or physiologic degeneration, extrinsic insults, and intrinsic insults. In the auditory system the extrinsic component is called nosocusis, which includes hearing loss due to otologic disease, hazardous noise exposure, acoustic trauma, and ototoxic agents. The intrinsic component, called sociocusis, indicates the wear-and-tear effects of the everyday sounds of normal living.[2] Goycoolea and co-workers showed that both nosocusis and sociocusis are avoidable in the quiet environment of Easter Island.[3]

Hearing clearly steadily worsens with age. The rate of change, however, is not linear, is highly variable, and is only weakly associated with chronologic age per se. For example, in comparing the change in hearing thresholds of the Framingham Heart Study cohort, less than 10% of the variance was accounted for solely by age.[4] This suggests that other factors affect hearing more than age alone. In our industrialized society, it is difficult to escape from noise pollution. It is likely that much of the variance in levels of presbycusis is due to unmeasured effects of noise damage, which is clearly more common than other forms of ototoxicity. The effects of systemic disease are still incompletely understood, and we will discuss these.

Pathology

Four types of presbycusis have been described, based on histopathology, and different mechanisms have been postulated for each.[5] These types are sensory (hair cell loss), neural (ganglion cell loss), metabolic (strial atrophy), and cochlear conductive (stiffness of the basilar membrane). Our longitudinal studies of the Framingham Heart Study cohort are providing insight into the progression of presbycusis. Sensory presbycusis is the dominant type, affecting more than 75% of the group. The magnitude of the presbycusis varies so widely, however, that it is difficult to ascribe what proportion of the loss is due to pure aging and what proportion to acquired loss from noise exposure, ototoxicity, and the effects of systemic disease. We are currently examining the children of the cohort in an attempt to identify a genetic component that might explain some of this variability. Presbycusis is well known to be more prevalent in

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selected families than in others. The genetic basis for this variation is not known.

Environmental noise exposure is a major risk factor for sensory presbycusis. The well-known effects of hazardous occupational and recreational noise exposure contribute substantially to an earlier onset of hearing loss than would be expected from aging alone. It is difficult, however, to ascribe portions of the hearing loss separately to noise and to aging, which is being attempted in various compensation litigations. We now know that gerbils raised in quiet have as much hearing loss with age as groups of noise-reared animals, and some have even more.[6] Of interest, the variation in hearing level of the quiet-reared animals is far greater than that of the noise-exposed group, which suggests some degree of homogenization due to noise. Given that noise and aging both affect the high-frequency regions of the cochlea, we suggest that sensory presbycusis be considered as the cumulative effects of either or both agents and that noise simply accelerates the time course of sensory presbycusis.

The recent discovery that the outer hair cells are motile has provided an explanation for the source of the cochlear amplifier, that is, the nonlinear biologic mechanism that increases our sensitivity to sounds of low intensity without enhancing loud sounds.[7] The outer hair cells are stimulated by the mechanical vibration of sound waves to contract within the electrical environment of the cochlea. The rate of contraction exceeds that of all known contractile systems. A manifestation of that process is the generation of low-amplitude signals that may be detected in the ear canal known as otoacoustic emissions. Otoacoustic emissions may be generated by specific auditory inputs, the most clinically useful of which are the distortion-product otoacoustic emissions. Equipment to measure distortion-product otoacoustic emissions is now commercially available. Alterations in these emissions can be detected well in advance of clinically detectable changes in auditory thresholds. The measurement of these emissions is useful for monitoring patients receiving chemotherapy or other ototoxic medications.

Neural presbycusis is uncommon, accounting for less than 2% of the cases in the Framingham Heart Study cohort.[8] Unfortunately, the term "nerve deafness" is firmly entrenched in the lay literature and popular usage, even though it has led to frequent misunderstanding of the potential of rehabilitation. The term is a shortening of "sensorineural," which has been used to indicate nonconductive hearing loss of an undetermined site of lesion. With contemporary audiometric techniques that reveal the site of a lesion, this term will be used less often. Given that the vast majority of hearing impairment is due to the loss of the motor and sensory hair cells, to imply that neural lesions are involved is inappropriate and misleading. Amplification through modern hearing aids provides substantial benefit to people with sensory hearing loss due to hair cell loss. A person with a pure neural lesion has limited benefit from amplification, whether the lesion is in the eighth nerve (for example, an acoustic neuroma), in the brain stem (as in multiple sclerosis), or in the midbrain (as in Alzheimer's disease).[9] Thus, the use of contemporary techniques to identify the site of a lesion and the use of appropriate terms are important so that patients and health care professionals alike may be correctly oriented toward optimal treatment or rehabilitation.

The stria vascularis is the metabolic pump that generates the strongly negative endocochlear potential. Strial atrophy is seen histologically in many people with a flat hearing loss, that is, elevated thresholds for all frequencies. We have shown that poor low-frequency hearing, which is typical of strial or metabolic presbycusis, is associated with cardiovascular diseases (heart attacks, stroke, intermittent claudication) and that this effect is present in both men and women but is stronger in women.[10] We postulated that postmenopausal estrogen decline might be a factor in this association in women. In examining the hearing of a small group of older women in a separate study (unpublished data, September, 1996), however, we found no association of postmenopausal estrogen replacement therapy with hearing thresholds in otherwise healthy women. Although it appears that low-frequency presbycusis is associated with general cardiovascular disease, and it is known that postmenopausal estrogen replacement therapy is generally protective against cardiovascular disease in women, we cannot suggest, based on these data, that this therapy would prevent strial presbycusis.

Cochlear conductive or mechanical presbycusis is characterized by a sharply sloping loss and normal hair cell and strial function. Clinically, this audiometric pattern is uncommon and is more of theoretic than practical interest, as the rehabilitative implications of this subtype are not different from those of the sensory or strial forms.

Diagnosis

Hearing loss is often a silent disorder, characterized more by what is missed than what is heard. In the vast majority of cases, family and friends are more aware of the problem than the patient. In many instances, the hearing loss is accompanied by tinnitus—the perception of a sound in the ears or head that is often described as a ringing sound. Tinnitus is usually a sign of hearing loss and should be assessed to exclude treatable disease as a cause.

Although it would seem prudent for health care professionals to screen for one of the most prevalent chronic conditions affecting older patients, this is unfortunately not the practice with hearing loss identification.[11] Moreover, even when older patients have discussed their hearing difficulties with their primary care physicians, they are often told that their hearing loss is minor or that it cannot be improved with a hearing aid.[12] When we consider the adverse effects of hearing loss on the quality of life of older persons and that such effects are reversible with hearing aids, it is surprising that in-office

Question	Yes	No	Sometimes
1. Does a hearing problem cause you to feel embarrassed when meeting new people?	☐	☐	☐
2. Does a hearing problem cause you to feel frustrated with talking to members of your family?	☐	☐	☐
3. Do you have difficulty hearing when someone speaks in a whisper?	☐	☐	☐
4. Do you feel handicapped by a hearing problem?	☐	☐	☐
5. Does a hearing problem cause you difficulty when visiting friends, relatives, or neighbors?	☐	☐	☐
6. Does a hearing problem cause you to attend religious services less often than you would like?	☐	☐	☐
7. Does a hearing problem cause you to have arguments with family members?	☐	☐	☐
8. Does a hearing problem cause you difficulty when listening to TV or radio?	☐	☐	☐
9. Do you feel that any difficulty with your hearing limits or hampers your personal or social life?	☐	☐	☐
10. Does a hearing problem cause you difficulty when in a restaurant with relatives or friends?	☐	☐	☐

Figure 1.—This Hearing Handicap Inventory for the Elderly–Short Form hearing questionnaire is an effective screening tool for hearing loss.[20]

screening for hearing loss is not common practice. The short form of the Hearing Handicap Inventory for the Elderly (HHIE-S) consists of ten questions that can be answered quickly by most seniors (Figure 1).[13] This is an excellent screening instrument for substantial hearing loss.

The medication history should be explored to determine possible ototoxicity. The use of aminoglycoside antimicrobial agents, cisplatin, loop diuretics, or anti-inflammatory agents may contribute to hearing loss.

The findings of physical examination of the ear canal, tympanic membrane, and middle ear are normal. The use of tuning forks, the whispered or spoken voice, or finger-friction tests is not effective or reliable in identifying hearing loss. Screening audiometry can be quickly and easily administered by a trained office nurse or medical assistant. The equipment needed for screening audiometry is light-weight and low cost. There are portable, battery-operated audiometers and even specially developed otoscopes with audiometric capabilities available for practitioners. We typically have our office nurse screen hearing at 1, 2, and 3 kHz at intensity levels of 25 dB (normal), 40 dB, and 60 dB. Failure at any one frequency at 25 dB for younger adults or 40 dB for senior adults suggests the need for referral for a complete audiologic evaluation by an otologist or audiologist. The identification of hearing impairment and the determination of hearing-aid candidacy serve to remove a hearing-impaired senior from isolation, withdrawal, and decreased quality of life. Physicians who provide primary care to elderly persons should screen for hearing impairment with the HHIE-S, by screening audiometry, or both.

Central auditory tests are widely available and should be used when the possibility of early dementia exists. We have shown that poor performance on a standard central auditory test, Synthetic Sentence Identification With Contralateral Competing Message, precedes the clinical onset of dementia.[14] With the possibility of treatments to forestall the progression of Alzheimer's disease, early identification is of great importance.

Imaging studies are not done except where the loss is unilateral or considerably asymmetric or where tinnitus is unexplained by an audiogram. Screening magnetic resonance imaging using the T2 fast-spin echo technique provides superb visualization of the eighth nerve and brain stem and can detect tumors in the millimeter range, even before hearing is affected.[15]

A metabolic evaluation is indicated if a patient has not had a recent health examination. Diabetes mellitus, hypertension, and hyperlipidemia should be excluded as cofactors. Patients receiving renal dialysis often have poorer hearing than would be expected from age alone. The use of diuretics is known to affect strial function, and certain disorders, such as aminoglycoside toxicity, affect both the kidneys and the inner ear.

Effects of Presbycusis

Presbycusis affects both of the critical dimensions of hearing; namely, it reduces threshold sensitivity and reduces the ability to understand speech. The loss in threshold sensitivity is insidious in onset, involving the highest frequencies initially and slowly progressing to become clinically manifest in the fifth to sixth decades. Most often, patients with presbycusis do not express dif-

ficulty in hearing per se but are more likely to report problems in understanding speech. The common complaint of "I can hear, but I can't understand" reflects the encroachment of the sensitivity loss into the important high-frequency speech range (0.5 to 3 kHz). The louder and lower frequency segments of speech, such as the vowels, can be heard, but the high-frequency voiceless consonants, such as *t*, *p*, *k*, *f*, *s*, and *ch*, are not heard due to the high-frequency sensitivity loss. A person then confuses and misinterprets what is being spoken: "Did you say 'mash,' 'math,' 'map,' or 'mat'?"

The difficulties in understanding speech not only may reflect a sensitivity loss but also may be due to the effects of central nervous system auditory deterioration.[1] Seniors often have more difficulty in understanding speech than younger persons with comparable sensitivity loss. When pure-tone sensitivity loss is held constant and speech understanding is evaluated by decade, a systematic decrement of speech intelligibility is shown with increasing age. Moreover, whenever the speech message is degraded, an elderly listener's difficulties increase dramatically more than younger listeners. Older persons have considerably greater problems than younger persons in understanding rapid speech, foreign accents, or speech transmitted through poor transmitting equipment or under unfavorable acoustic conditions. Such problems are thought to be due to a central integrative and synthesizing hearing disability that reflects a progressive deterioration of the central nervous system. Therefore, a senior person's problems in understanding speech may be due to cochlear hair cell deterioration (sensory presbycusis), auditory neural deterioration (neural presbycusis), or central auditory processing deterioration (or all three).

Mulrow and colleagues demonstrated the effect of presbycusis on quality of life and found reversible changes through hearing-aid use.[16]

Treatment

Prevention

Although some degree of sensory presbycusis is inevitable, it may be minimized by avoiding exposure to hazardous noise. If noise cannot be avoided, the use of suitable hearing protection is essential. Inserted earplugs provide about 15 to 25 dB of attenuation and may permit people to work in otherwise hazardous areas with a reduced risk of damaging their hearing. The effects of noise accumulate over a lifetime, and exposure to gunshot noise and loud music during adolescence will contribute to communication difficulties in the senior years. Unfortunately, many people are not farsighted enough to act prudently in this regard.

The use of ototoxic agents such as cisplatin for cancer chemotherapy and aminoglycoside antimicrobial compounds may cause any degree of hearing loss, from a mild high-frequency loss indistinguishable from sensory presbycusis to profound hearing loss and deafness. Although the search for protective agents continues, diligent monitoring provides the best method for early detection and the opportunity to modify the treatment plan. Some persons have specific mitochondrial defects that appear to predispose them to catastrophic hearing loss from the use of gentamicin sulfate.[17]

Risk factors for cardiovascular disease and cardiovascular disease itself affect hearing to some extent. Hypertension, hyperlipidemia, and diabetes mellitus have all been associated with excessive hearing loss. Therefore, it is logical that maintaining good general health would minimize the risk of hearing loss due to systemic disease. High-lipid diets are associated with poorer hearing.[18]

Rehabilitation

Although hearing loss due to conductive deficits (such as otosclerosis, otitis media, and eardrum perforations) can be most often successfully treated with medical or surgical intervention, the most common type of hearing loss is caused by dysfunction in the cochlea or associated neural structures. Of all patients with cochlear hearing loss, less than 5% can be helped medically. Consequently, the most important rehabilitative approach for hearing-impaired elderly persons is the hearing aid. Hearing aids are the principal resource for improving communication and reducing hearing handicaps in persons with sensorineural hearing loss. Unfortunately, only 10% of people who might benefit from an aid actually own one, which indicates a substantial underservice.

A hearing aid is a miniature personal loudspeaker system designed to increase the intensity of sound and deliver it to the ear with as little distortion as possible. Important improvements in hearing-aid design have made possible greater flexibility in selecting and fitting hearing aids for the typical hearing loss patterns associated with aging. In the past decade, an increase in technologic innovations has occurred that has made possible a wide assortment of hearing aids both in physical size and technologic advancement. Current hearing aids include devices that fit behind the ear, in the ear, in the canal, and most recently, completely in the canal. Because many persons unfortunately associate hearing loss with the "stigma" of aging, the introduction of the smaller devices that fit entirely in the ear canal has had obvious appeal. Those seniors with dexterity problems or vision impairments are often unable to insert and adjust the smaller aids properly and are better served with larger hearing aids. The hearing aid fitter-dispenser should review such issues with the hearing-impaired person during the prefitting session.

Technologic advances in hearing aids now offer patients a wide variety of amplification options. Hearing aids no longer merely provide linear amplification, but may include compression circuitry to reduce the amplification for loud sounds, automatic loudness-adjusting circuits that automatically decrease the amplification of continuous background sounds, and also

hearing aids without volume controls that automatically increase the loudness of soft sounds while decreasing loud-level inputs. Because a single amplification paradigm may not be of benefit for all listening situations, hearing aids are available that include several programs for use at the listener's discretion. A person may choose a wide-frequency amplification for quiet environments, another program that eliminates low frequencies for noisier situations, and a program specifically suited for telephone use. These hearing aids are digitally programmed by an external programmer through the use of a controlling microchip within the hearing aid itself. Individual programming of the hearing aid enables the dispenser to make substantial electroacoustic modifications to an individual wearer's needs. Such multimemory hearing aids typically include a user-operated remote control to facilitate program or volume changes. Some hearing aids now incorporate several microphones, one for use to improve directionality in background noise situations and another for use in other environments where a broad range of acoustic input is desired. The most recent introduction in hearing-aid technology is the fully digital instrument, which has the processing power of a desktop personal computer and can be fit into the small canal-sized instruments. These aids have many features not available in analogue hearing aids and will undoubtedly provide hearing-impaired persons with improved hearing in future years.

The new innovative hearing-aid systems do require a higher level of training and sophistication on the part of the user and the fitter-dispenser. In addition, these new amplification systems are considerably more expensive than conventional hearing aids. The digital in-the-canal aid currently costs about $2,500 for one aid, and binaural aids are typically more beneficial. Neither Medicare nor most insurance carriers provide financial coverage for hearing aids. The specific hearing needs, lifestyle, and adaptability of a hearing-aid wearer must be taken into account during the prefitting process.

Hearing-Aid Candidacy

Once a hearing loss has been identified and it is clear that medical or surgical treatment is not indicated, referral should be made to a certified clinical audiologist. The clinical audiologist is a university-trained professional in the nonmedical management of hearing loss, whether with hearing-aid amplification, rehabilitation therapies, assistive listening devices, or a combination of rehabilitative approaches. Although some hearing-aid dealers are relatively skilled in evaluating hearing aids, others possess only minimal training or are more oriented to sales. Many states, in fact, require that a hearing-aid dealer meet only the minimum requirement of being 18 years old and passing a state licensing examination; there are typically no education requirements. Clinical audiologists, on the other hand, hold at least a master's degree in the evaluation and rehabilitation of hearing loss. Audiologists are uniquely qualified to provide a full range of auditory assessment and rehabilitative services to elderly persons.

After the necessary interview and evaluation, an audiologist-dispenser will recommend the type of hearing aid or aids, specify the acoustic requirements of the aids, and provide training in the use of amplification. The possible advantages and limitations of hearing aids are reviewed, and follow-up is provided during the initial trial and after purchase. It is usual to provide patients with a free or low-cost hearing-aid trial period of 30 days before purchasing the aid(s). This trial period gives patients the opportunity to wear the aid(s) in their own home and social environment to determine their satisfaction.

Hearing-Aid Prognostic Factors

Adapting to hearing-aid use is at times difficult because successful adjustment depends to a large degree on a patient's personality dynamics. Often a senior adult is resistant to amplification because of the social stigma associated with hearing loss. Because our culture unfortunately views hearing loss as a consequence of aging, resistance to a hearing aid is inevitable. Factors of motivation, personal adjustment, and family support can be instrumental in hearing-aid satisfaction.

Assistive Listening Devices

Although substantial improvements have been achieved in hearing-aid design and application, few hearing-impaired persons can ever come close to achieving "normal" auditory function with the use of a hearing aid alone. The inherent physiologic restrictions imposed by age-related hearing loss, coupled with the electronic constraints of hearing aids, renders normal hearing impossible, especially considering the levels of noise and background interference found in most public places. The amplification of unwanted sounds (such as several speakers in groups, background noise, ventilation) by hearing aids often causes the desired message to be rendered unintelligible.

Assistive listening devices compose a growing number of situation-specific amplification systems designed for use in difficult listening environments. They commonly use a microphone placed close to the desired sound source (such as a television, theater stage, or speaker's podium), and sound is directly transmitted to the listener; transmission methods include infrared, audio loop, FM radio, or direct audio input. Such transmission of sound directly to the listener improves the signal-to-noise ratio. That is, the desired sounds are enhanced, and competing extraneous noises are decreased, thus permitting improved understanding. These assistive listening devices are becoming more available in churches, theaters, and classrooms, enabling hearing-impaired seniors to avoid the isolation imposed by the inability to hear a sermon, play, or public address.

Amplified telephones, low-frequency doorbells, amplified ringers, and closed-captioned television decoders are just a few examples of the devices currently available for hearing-impaired persons for everyday use. Flashing alarm clocks, alarm bed vibrators, and flashing smoke detectors provide valuable help for

severely hearing-impaired persons.

Although the treatment of hearing impairments with hearing-aid amplification, assistive listening devices, and aural rehabilitation therapy does not "cure" the impairment or restore hearing and communicative efficiency to normal, the use of such approaches does represent the best treatment to date. They will improve the ability of most older persons to communicate and reduce the handicapping consequences of hearing loss.

Medical Therapy

Once thought to be untreatable, some cochlear lesions are now responding to medical therapy. About a third of people with sudden hearing loss recover hearing. Most people with autoimmune hearing loss recover substantial amounts of the loss with corticosteroid and other anti-immune treatment, such as methotrexate and plasmapheresis. For the vast majority of people with presbycusis, however, definitive treatment must await the results of our ongoing research programs in hair cell regeneration.[19] This section will undoubtedly be expanded in the next decade or two.

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SUCCESSFUL AGING

Seeing Into the Future

Vision and Aging

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The leading causes of visual impairment in North Americans are age-related, but appropriate care can preserve useful vision for most older adults. Cataract surgery is highly successful. Early detection and treatment of glaucoma can prevent vision loss. Laser treatment is remarkably effective against diabetic retinopathy. Vision loss due to macular degeneration cannot be delayed in all patients, but low-vision rehabilitation can maximize the usefulness of remaining sight.

(Kalina RE. Seeing into the future: vision and aging. In: Successful Aging. West J Med 1997; 167:253–257)

Vision has been considered the most precious of the senses, as treasured as life itself. Public opinion surveys repeatedly have shown that the United States public fears blindness second only to cancer. A population-based study showed that functional visual impairment increased from 7% at age 71 to 39% in patients aged 90 years and older.[1] Age-related loss of vision affects central visual acuity, peripheral vision, contrast sensitivity, and color vision.

The ramifications of a high prevalence of visual impairment in an aging population are many. Care and services provided for persons who are blind or have visual impairments cost the nation in excess of $22 billion each year. Visual impairment can lead to loss of self-esteem and loss of independence in activities of daily living, automobile driving, and general mobility. Visual impairment has been shown to be a risk indicator for reduced survival.[2]

Huge advances have been made in preserving vision for citizens of industrialized countries over the past several decades, and successful aging with good vision is now possible for many who would have suffered visual impairment in the past. Nevertheless, the well-documented aging of the US population threatens to result in a large number of visually impaired older adults.

Physiologic Aging of the Eyes and Visual System

The eyelids share the general loss of tone and substance that is common to other aging cutaneous tissues. The result is an acquired laxity that can result in ptosis of the eyelids and eyebrows, redundancy of the skin of the eyelids, and eyelid malpositions. Although these disorders rarely threaten vision, they frequently contribute to discomfort or disfigurement. Fortunately, oculoplastic surgical techniques have evolved to correct most of these states readily.

Both benign and malignant tumors occur on the eyelids. Basal cell carcinoma occurs more frequently on the lower eyelid and inner canthus than anywhere else on the body. Early detection leads to excellent treatment results, and prevention should be directed to limiting sun exposure.

Tear production declines throughout life.[3] Mild tear deficiency may produce annoying symptoms of foreign body sensation and burning while severe dryness can be associated with corneal ulceration and opacity, resulting in vision loss. Tear deficiency is a frequent problem for older adults, especially when the eyes are exposed to wind, heat, or low humidity. Symptomatic relief is obtained with one of the many tear replacement products available commercially. Severe cases

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may benefit from occlusion of the puncta of the lacrimal drainage system.

Intraocular pressure increases with age in most people.[4] Elevated intraocular pressure is a significant risk factor for the development of the characteristic optic nerve damage and consequent visual loss known as glaucoma. Some persons develop glaucoma without measurable elevation of intraocular pressure.

The human lens grows throughout adult life but the globe does not, resulting in shallowing of the anterior chamber.[5] The changes in crystalline lens dimensions with age, the associated change in the geometry of zonular attachments, and changes in viscoelastic properties of the lens capsule and lens matrix result in a progressive loss of accommodative ability from youth to middle life.[6] The loss of accommodation reaches critical proportions when the ability to read at arm's length is lost, usually about age 45 years. The onset of presbyopia is often the most specific evidence of the aging of the human body to its inhabitant. Most accommodative facility has been lost by 55 years of age.

The delicate collagen framework of the vitreous gel often collapses in middle life to form aggregates that are sufficiently large to cast shadows on the retina. These vitreous "floaters" do not impair visual acuity but can be a source of annoyance to some persons. When only a thin layer of cortical vitreous remains adjacent to the retina, the gel may collapse inward, an event known as posterior vitreous detachment (PVD). As the posterior vitreous detaches from the retina, patients experience light flashes (photopsia). New floaters, including a large shadow caused by glial tissue detached from the surface of the optic disc, appear suddenly. The acute symptoms of PVD subside over a time period ranging from several days to several months. More than 60% of persons over age 70 have clinical evidence of PVD. All patients with symptoms of PVD (acute onset of flashes and floaters) deserve an urgent dilated ophthalmologic examination to rule out retinal tears.

Although reduced retinal illumination due to pupillary narrowing associated with aging and interference with light transmission through the ocular media, particularly the lens, probably account for much of the loss of visual function associated with physiologic aging, retinal cell loss also may play a role.[7] The rods of the central retina, responsible for vision under conditions of dim illumination, appear to be preferentially vulnerable to aging whereas foveal cones remain remarkably stable in number. Cell loss in the ganglion cell layer and retinal pigment epithelium appear to parallel the rod loss.[8]

Whether or not any visual disturbances are specific for Alzheimer's disease remains uncertain because of the lack of objective evidence and the difficulty of obtaining reliable subjective responses from affected persons.[9] One small study failed to find a difference in ganglion cell counts in postmortem retinas from patients with Alzheimer's disease and age-matched controls.[10]

Leading Causes of Visual Impairment in Elderly Persons

Cataract

Cataract is a clouding of the crystalline lens. Contrary to popular belief among laypersons, it is neither a growth ("a film") nor a deposition of some foreign substance but rather a loss of transparency due to protein aggregation and the scattering of light. Although the onset of cataract can be influenced by factors such as trauma, diabetes mellitus, drugs, and other ocular disorders, the vast majority of cataracts currently are attributable to no cause other than aging. In one rural community in the United States, visually important cataract was reported in 3.9% of men and 10.0% of women between the ages of 55 and 64, increasing to 38.8% of men and 45.9% of women 75 years of age or older.[11]

At present no proven medical or dietary measures will prevent or retard cataract formation. Because there are suggestions that long-term exposure to sunlight and UVB radiation may influence cataract development, wearing UVB-blocking sunglasses in bright sunlight is prudent. A broad-brimmed hat or cap also protects the eyes and shades the skin of the face from neoplasm-inducing radiation as well.

Cataract surgery is the most frequently performed surgical procedure in the older-than-65 age group and, if measured in terms of desired results (improved vision), the most successful. More than 85% of patients undergoing cataract surgery note improvement in function and satisfaction with vision.[12] Patients with visually important cataracts in both eyes note further improvement after successful surgery in the second eye.

Surgical intervention is indicated when visual function falls below that required to meet a patient's needs and when removal of the cataract is likely to improve vision. Modern cataract surgery is not dependent on the stage of development of the cataract and can be done at any time, but surgery is indicated only when vision is substantially impaired and cannot be corrected by other means.

Most cataract surgery in this country is done under regional or local anesthesia in an ambulatory setting. Under microscopic control through a small incision, the surgeon removes a portion of the anterior lens capsule, the lens nucleus, and the lens cortex and then inserts into the capsular bag a lens implant of a power based on preoperative measurements. Most patients have improved vision early in the postoperative period. Complications are rare but can be vision-threatening and can lead to blindness in a monocular patient.

Contrary to popular belief, cataract surgery always requires invasive surgery and never is accomplished by the use of a laser alone. Opacification of the residual posterior capsule, however, occurs in many patients in the months and years following cataract surgery. The opacified capsule can be opened with a neodymium:yttrium-aluminum-garnet laser, restoring vision to preopacification levels. Laser capsulotomy is associated

TABLE 1.—*Frequency of Screening to Identify Patients at Risk for Glaucoma**

Age, yr	Asymptomatic African Americans	Other Asymptomatic Patients
20–39	Every 3–5 yr	Less frequently than every 3–5 yr
40–64	Every 2–4 yr	Every 2–4 yr
≥65	Every 1–2 yr	Every 1–2 yr

*From the American Academy of Ophthalmology.[14]

TABLE 2.—*Eye Examination Schedule for Persons With Diabetes Mellitus**

Age of Onset of Diabetes Mellitus, yr	Recommended Time of First Examination	Routine Minimum Follow-up†
0–30	5 yr after onset	Yearly
≥31	At time of diagnosis	Yearly
Before pregnancy	Before conception or early in first trimester	3 months

*From the American College of Physicians.[17]
†Abnormal findings will dictate the need for more frequent follow-up examinations.

with a low but significant rate of vision-threatening complications and, like cataract surgery itself, should be done only to relieve visual impairment.

Glaucoma

Glaucoma is thought to affect nearly 2.5 million persons in the United States. An estimated 80,000 North Americans are legally blind from glaucoma, and many more are visually impaired.[13]

Primary open-angle glaucoma accounts for at least 90% of all cases, and primary angle-closure glaucoma occurs in less than 10%. Both types of glaucoma increase in prevalence with age, and both have a familial incidence. Primary angle-closure glaucoma is more prevalent among Asians, and primary open-angle glaucoma is more common in African Americans. Elevated intraocular pressure in both forms of glaucoma is caused by obstructed outflow of aqueous through the angle of the anterior chamber. In primary angle-closure glaucoma there is synechial or appositional closure of the angle by the iris; in primary open-angle glaucoma the mechanism of obstruction is poorly understood.

Because vision loss and optic nerve damage due to glaucoma usually are irreversible, early diagnosis and treatment are essential. Definitive treatment of acute primary angle-closure glaucoma is urgent and requires the creation of an opening in the iris (iridotomy), usually by the use of a laser. Laser iridotomy often is curative, but in some cases, permanent angle damage may require medications or further surgical therapy for the long-term control of intraocular pressure.

The treatment of primary open-angle glaucoma is directed at lowering the intraocular pressure through some combination of medical treatment, laser surgery, and incisional surgery. Once a diagnosis of primary open-angle glaucoma is made, lifelong care will be required but vision will be retained in most compliant patients.

Because it is so frequent for vision loss due to glaucoma to occur in the absence of increased intraocular pressure on spot checks, glaucoma screening by intraocular pressure checks alone no longer can be recommended. Mass screenings that include either or both visual field testing and optic disc examination for cupping are cumbersome and require advanced technology and skill. Although primary care physicians should be alert to risk factors for glaucoma and should be familiar with the appearance of a glaucomatous optic disc, periodic professional eye examinations are the most efficient approach at present to early detection and diagnosis. Because glaucoma often is asymptomatic until far advanced, periodic eye examinations are recommended every three to five years for African-American patients between ages 20 to 39, for all patients every two to four years from ages 40 to 64, and every one to two years for those aged 65 and older (Table 1).[14] Patients with a history of glaucoma in first-degree relatives require earlier and more frequent monitoring.

Diabetic Retinopathy

The incidence of diabetic retinopathy is related directly to the duration of the diabetic state. Nearly all persons with diabetes mellitus will have some retinopathy after 20 years, a life expectancy often exceeded through modern diabetes management. Only a generation ago, most patients with diabetes surviving 20 years or more suffered vision loss, often severe. The intuitive belief that better control of serum glucose levels delays the onset and lessens the severity of retinopathy has recently been confirmed.[15] Nevertheless, risk still exists for all patients with diabetes, even those under tight control.

Vision loss due to diabetic retinopathy results from either the proliferation of new blood vessels with vitreous hemorrhage and traction retinal detachment or nonproliferative retinopathy with leakage from damaged retinal blood vessels and resultant macular edema. Severe vision loss from both proliferative and nonproliferative diabetic retinopathy can be prevented by timely laser treatment.

The treatment of diabetic retinopathy is remarkably effective. The combined results of the Diabetic Retinopathy Study and the Early Treatment Diabetic Retinopathy Study landmark clinical trials, sponsored by the National Eye Institute, show that with prompt treatment as much as 98% of severe vision loss or blindness from diabetic retinopathy can be prevented.[16] Patients who suffer loss of vision as a result of vitreous hemorrhage or retinal detachment because timely laser treatment was not done or because laser treatment failed often can have some vision restored by vitrectomy (microsurgical removal of the vitreous) and reattach-

ment of the retina. Preventing these complications by laser surgery is much preferred, however.

All patients with diabetes mellitus require periodic screening examinations for the presence of diabetic retinopathy so that laser surgery can be done when first indicated and vision can be preserved. The currently recommended times for initial and follow-up examinations are detailed in Table 2.[17]

Accurate screening for diabetic retinopathy requires dilation of the pupils. Although other practitioners probably could be trained adequately to detect diabetic retinopathy through dilated pupils, ophthalmologists are currently the only group that regularly exercise this practice pattern. In the future it may become practical to image the fundus for viewing by an expert at a remote location.

Macular Degeneration

The macula is the specialized centrally located area of the retina that is uniquely capable of tasks requiring the detection of fine detail such as reading and the recognition of facial features. Although some forms of macular degeneration strike young persons, the great preponderance of cases are related primarily to aging.

Age-related macular degeneration is the leading cause of irreversible severe vision loss in persons older than 60. It is present in 30% of persons older than 75 and will develop in 23% of the remainder within five years.[18] Age-related macular degeneration is nearly exclusively a disorder of white persons and is more frequent in women than in men. Cases tend to cluster in families. Smoking and cardiovascular disease are known risk factors.[19] Sunlight exposure has been suggested but not proved to be an associated factor.

Age-related macular degeneration is characterized by the presence of drusen, yellow-white deposits of extracellular material containing photoreceptor debris external to the retinal pigment epithelium. Some forms of drusen are inherited in an autosomal dominant pattern. The presence of drusen alone does not make a diagnosis of age-related macular degeneration, but they are associated with disturbances of the retinal pigment epithelium that may lead to atrophy with vision loss, constituting nonexudative (dry) age-related macular degeneration. Drusen also predispose to the development of choroidal neovascularization with loss of vision due to subretinal exudation of fluid and blood, the exudative (wet) form of age-related macular degeneration. Age-related macular degeneration typically is bilateral, but vision loss may be asymmetric.

Vision loss due to nonexudative age-related macular degeneration typically is slowly progressive, and no known treatment will influence this course. A large clinical trial, the Age-Related Eye Disease Study, is under way to assess the influence of vitamin and mineral dietary supplements, but at this time no accepted clinical trial results are available to support the intense marketing of these products to the public.

Conversion of the nonexudative form of age-related macular degeneration to the exudative form is heralded by a sudden loss of central vision, often associated with changes in the size and shape of perceived objects. A series of randomized clinical trials known as the Macular Photocoagulation Study showed that focal laser photocoagulation directed to choroidal neovascularization well defined on fluorescein angiography was capable of stabilizing vision and leading to an outcome better than a natural history.[20] Less than 20% of patients with exudative macular degeneration satisfy the criteria for this treatment, however, benefits are limited, and recurrences after treatment are frequent.

Age-related macular degeneration impairs only the central vision, not the peripheral visual fields. All but the most severely affected patients are able to maintain relatively normal mobility, but independence in activities of daily living can be substantially altered unless special techniques and devices are acquired and used.

Coping With Visual Impairment

Visual impairment may be correctable by optical devices or surgery or noncorrectable due to ophthalmologic or neurologic states. Noncorrectable visual impairment often is called low vision. Low vision lies between normal vision and blindness (or near-blindness) wherein patients require special mobility training and the substitution of other senses for vision (such as learning Braille). Patients with low vision may appear outwardly normal to others but may be unable to read or recognize their friends in public.

Patients with low vision should be encouraged and assisted to maximize the usefulness of their remaining vision.[21] Powerful spectacles, handheld or stand magnifiers, and closed-circuit video units or computers are the most frequently used reading devices. Proper illumination intensity and direction are critical. Spot distance viewing is facilitated by a pocket telescope. A variety of clever personal and household aids for the partially sighted add to independence and to the enjoyment of life.

Physicians may inadvertently contribute to the sense of disappointment or despair patients experience with visual impairment. The lack of effective medical or surgical treatment for disorders such as macular degeneration does not mean that nothing more can be done. Physicians should be aware of community resources for the visually impaired and encourage patients to use them.

Horizons

Aging of the "baby boom" population over the next several decades will pose great challenges for the prevention and treatment of age-related visual impairment, but innovative research offers promise. New drugs may delay the onset of visually disabling cataract beyond the usually expected life span. Genes have been identified that lead to certain forms of glaucoma. Improvements in diabetes management will reduce the incidence of

retinopathy, and new retinal imaging techniques may facilitate screening. The genetic basis for age-related macular degeneration is being sought to open the door to new prevention strategies. Macular degeneration research also will be directed toward the inhibition of choroidal neovascularization and toward retinal cell transplantation. Rehabilitation techniques and devices will become more widely available to the hidden population of the visually impaired.

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SUCCESSFUL AGING

Preserving Mobility in Older Adults

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Age-related loss of strength contributes to impaired mobility and increases the risk of falls. Recent research has focused on 2 approaches to preventing age-related loss of strength—promoting physical activity and exercise (especially strength training) and using trophic factors to enhance muscle performance. Epidemiologic evidence strongly supports a role of regular physical activity in successful aging by preserving muscle performance, promoting mobility, and reducing fall risk. Randomized controlled trials provide convincing evidence that strength and endurance training improve muscle performance in older adults. Evidence is rapidly accumulating from randomized trials that endurance, strength, and balance training promote mobility and reduce fall risk, though exercise effects differ according to the type of exercise, details of the exercise program, and the target group of older adults. Because lifetime regular physical activity is recommended for all older adults, a reasonable strategy (especially for weak adults) is an activity program that includes strength training. In contrast, insufficient evidence exists to recommend the long-term use of trophic factors to preserve muscular performance. An intervention that merits additional study is avoiding the use of psychoactive drugs because drugs like benzodiazepines appear to be risk factors for inactivity and may have unrecognized direct effects on muscular performance. Because chronic illness is a risk factor for inactivity and disuse muscle atrophy, randomized trials comparing strength training with other interventions would be useful in understanding whether strength training has advantages in preserving muscle performance and improving health-related quality of life in a variety of chronic illnesses such as depressive illness.

(Buchner DM. Preserving mobility in older adults. In: Successful Aging. West J Med 1997; 167:258–264)

We are all interested in preserving the health of our largest tissue: muscle. Muscle accounts for 45% of body weight. If the roughly 450 skeletal muscles in our body (containing some 250 million muscle fibers) contracted all at once, they would produce a force of 25 tons.[1] In the healthy state, our muscles work remarkably well. They can be switched on within milliseconds. They convert chemical energy (either fat or carbohydrate) to mechanical work, with complete silence, at 40% efficiency (roughly the same efficiency of a diesel engine).[1] They can operate both aerobically and anaerobically. Muscle and its neural control are also remarkably "plastic." Muscle strength declines by a few percentage points with each day of strict bed rest. With physical activity, muscles hypertrophy. With practice, muscles contract just the right amount at just the right time.

Aging poses a challenge to preserving muscular performance. Scientific studies for more than 100 years have confirmed the obvious: skeletal muscle strength and coordination decline with age. This decline is partly responsible for the decline in mobility and an increased risk of falls.

In this article I review what is known about preserving skeletal muscular performance, in particular as it relates to preserving mobility and preventing falls in older adults. For the most part, I have ignored the many determinants of mobility and falls that do not involve skeletal muscle.

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ABBREVIATIONS USED IN TEXT

FICSIT = Frailty and Injuries: Cooperative Studies of Intervention Techniques
HR = heart rate
HRR = heart rate reserve
Vo_2max = maximum oxygen consumption

Conceptual Model and Terminology

Our conceptual framework for discussing mobility and falls comes from the Nagi model of disability.[2] The causes of disability (etiologic agents) are termed "risk factors." Their effects are measured at four levels:

- Pathology (or disease) is measured at the cell and tissue levels. Examples of measures of muscle at this level are the fiber cross-sectional area, the ratio of type I to type II fibers, and measures of muscle enzyme levels.
- Impairment (or physiologic impairment) is measured at the organ and organ system level. Measures of the physiologic capacity (physiologic reserve) of muscle include maximum force (strength), maximum power, and maximum oxidative capacity. We regard measures of physical fitness (muscle strength, aerobic capacity, anaerobic capacity, body composition, and flexibility) as measures of physiologic capacity. (Physiologic aspects of balance and coordination are also measured at this level, such as visual acuity, vestibular function, sensory neuropathy, and patterns of motor nerve innervation and stimulation of muscle.)
- Functional limitations are measured at the level of the whole person and describe behavioral ability. We restrict our interest in functional limitations to measures of mobility, such as measures of the ability to stand, sit, walk, turn, transfer, and climb. (Functional aspects of balance and coordination are measured at this level, such as the ability to stand on one leg, reach, hop, and hit a baseball.)
- Disability is measured at the level of the person-environment interaction. The environment encompasses both physical and social aspects. We focus on one measure of disability—fall incidence, which depends on the person-environment interaction.

The main risk factors of interest are physical activity and exercise. Physical activity is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure."[94] Exercise is "a subset of physical activity defined as planned, structured, and repetitive bodily movement done to improve or maintain one or more components of physical fitness."[94]

There is an intuitive causal chain across levels of the model. For example, inactivity causes muscle fiber atrophy, which causes muscle weakness, which in turn causes a slow unsteady gait, and this leads to falls. Feedback loops and other causal pathways are possible, however.

Two Obvious Interventions

Much of the research in the past decade on muscular performance and mobility has addressed either exercise or trophic factors.

Exercise

An obvious hypothesis is that exercise, particularly strength training, preserves muscular performance and mobility. This hypothesis was the rationale for what appears to be the first study of strength training in older adults published in 1961.[3] As obvious as this idea is, it was not seriously studied until the late 1980s. In the 1970s, the public health focus was on aerobic training, and strength training was not perceived as having much value.[4] It was questioned whether muscles in older persons could even respond to exercise training, as illustrated by a study in the early 1980s concluding that the muscles of older adults did not hypertrophy in response to strength training.[5]

Trophic Factors

The idea that hormones and anabolic steroids can enhance muscular performance is also an old idea. In 1977 a controlled trial of the anabolic steroid stanozolol claimed that anabolic steroids have been widely recommended in the management of debility in older adults with chronic diseases,[6] including diseases like osteoporosis.[7] In the 1980s, the emphasis shifted away from anabolic steroids to hormones, termed "trophic factors": estrogen, testosterone, and growth hormone. The interest in growth hormone was stimulated by the new industrial capacity to produce large quantities of hormone. A highly publicized study promoted interest in growth hormone by abetting the perception of growth hormone as an antiaging pill that removed skin wrinkles, decreased fat, and increased muscle mass.[8]

Major Research Findings and Recommendations of the Past Decade

Epidemiologic Plausibility of the Physical Activity Hypothesis

In the past decade, epidemiologic studies have addressed the association between all possible pairs of measurements in the causal chain of the physical activity hypothesis: physical activity improves muscle strength, which improves mobility, which in turn decreases the fall risk. A brief review of this evidence is important to arguing that regular physical activity (as opposed to only exercise programs) sustains mobility and prevents falls. The randomized controlled trial evidence for this hypothesis is not as comprehensive or complete and deals almost entirely with exercise programs as opposed to physical activity. The issue is of public health importance because most older adults who do sufficient activity to meet public health recommendations do not follow formal exercise programs.

Higher levels of physical activity are associated with greater muscular performance,[9–11] better mobility,[12–14] and a lower risk of falls.[15–17] There is some concern that high levels of physical activity may increase the fall risk[18] and fall injury risk.[19] Even after accounting for the morbidity due to falls, however, physically active adults appear to have less disability.[20]

Greater muscle strength is associated with better mobility[21–24] and a lower risk of falls.[25–27] The relationship between strength and mobility (as measured by gait speed) is nonlinear.[22,23] A nonlinear relationship makes intuitive sense: whereas professional athletes may be several times stronger than average adults, athletes do not walk several times faster than the average adult. Most of their strength is physiologic reserve not used during normal walking.

Finally, better mobility is also associated with a lower risk of falls.[16–18,28] Indeed, measures of mobility such as gait speed have moderately high correlations (0.5 to 0.6) with questionnaire measures of overall physical functional limitations and disability.[22,29]

Effects of Strength Training on Muscle Physiology

There is conclusive evidence that strength training increases skeletal muscle strength in older adults. A 1993 meta-analysis demonstrating the positive effect of training on strength was able to locate 18 studies.[32] The studies are not limited to the "young-old," as studies in 80- and 90-year-old adults also report increases in strength with resistance training.[30,31] Several studies show that muscular hypertrophy, including hypertrophy of type II fibers, occurs with training.[32]

High-intensity strength training produces substantially greater gains in strength,[32] which is consistent with basic principles of exercise physiology. High-intensity training involves training where muscles are exercised near or to the point of exhaustion, usually by setting the weight lifted at each repetition at 60% to 80% of the maximal weight a person can lift. Variation in the intensity of training across studies appears to be the major reason that exercise-related gains in strength vary over such a large range (20% to 200%). Other reasons for variation in reported results include differences in the duration of training and in the method used to measure strength. Even frail older adults can tolerate strength training at high intensity.[30,31]

Effects of Endurance Exercise on Muscle Function

The fitness response to an endurance training program in previously sedentary, healthy older adults is comparable to that of younger subjects[33] and usually on the order of 10% to 30% change over several months to a year. When older and younger adults are trained in the same program at the same relative intensity, their increments in maximum oxygen consumption (Vo_2max) are similar.[34] Healthy older adults can tolerate endurance training at high intensity (75% to 85% of heart rate reserve (HRR): HRR = 0.85 (HR max [maximum heart rate] – HR rest) + HR rest). The Vo_2max is the product of maximal cardiac output and maximal ability of muscle to extract oxygen. Long-term training appears to affect both components of the Vo_2max.[33]

Effects of Strength and Endurance Training on Mobility

Several randomized trials report that strength or endurance training (or both) improves gait speed by a modest amount.[35–37] Other trials have failed to find an effect.[38,39] The variation in results can be partly explained by a variation in frequency, duration, and intensity of training. Also, as explained earlier, if strength and endurance capacities are already adequate, further increases in capacity would not be expected to change relatively basic tasks like walking speed. This may explain why studies in nursing home patients have generally found an effect of exercise on gait speed[31,32,40] and why community trials may not.[38,39] Further research is needed to determine if exercise improves performance in high-level mobility tasks in elderly persons in the community, as existing research focuses on basic tasks.

The extent that strength training improves mobility by improving balance is unclear. A study comparing strength and balance training found that strength training had no effect on balance.[41] Like many other studies,[42–44] the study did report that balance training improved balance. It is possible that the effect of strength training on balance depends on the target group, with strength training improving balance in weak adults in a nursing home[31] but not in community adults.[39] It is likely that the effect of strength and endurance training on balance depends on the amount that balance is "stressed" during the exercises. Strength training that simultaneously stresses balance has been proposed.[45] A study of endurance training provided mild support to the hypothesis that the amount of movement during endurance training determines the effect of the training on balance.[35]

Effects of Exercise Training on Fall Risk

The National Institute of Aging funded a set of randomized trials, called FICSIT (Frailty and Injuries: Cooperative Studies of Intervention Techniques), in part to address whether exercise reduces the risk of falls. A meta-analysis of seven FICSIT trials reported that exercise reduced the fall risk by about 10% (adjusted fall incidence ratio, 0.90).[46] An interesting aspect of the findings is that balance training seemed to be particularly effective in reducing fall risk. A major strength of this meta-analysis was that it was preplanned, so that falls and case-mix variables were measured in a roughly comparable way at all FICSIT sites. The meta-analysis has been criticized for including interventions involving more than just exercise. Three studies of exercise have not reported a beneficial effect of exercise on fall risk,[47–49] though the statistical power of these studies was limited. The Musculoskeletal Injuries Group of the Cochrane Collaboration has planned a meta-analysis of this literature.

A commonly expressed concern of older adults and practitioners is that exercise will increase the risk of falls in older adults. Although some debate whether exercise

reduces fall risk, an extremely important conclusion from this literature is that exercise does not increase the overall risk of falls. This is not to say that older adults do not fall during exercise, because they do. The evidence shows that the short periods of increased risk of falls during exercise training is more than compensated for by a reduced risk of falls during the rest of the day.

Of course, the public health goal is to reduce the incidence of fall injuries. Falls are a surrogate outcome for fall injuries. It has not been shown that reducing the incidence of falls results in fewer fall injuries. That is, the possibility that exercise mainly prevents falls that do not result in injury has not been ruled out.

Exercise-related Injuries

A review of exercise intervention studies in older adults found that major injuries are rare in research studies.[50] Minor injuries are occasionally reported, but are almost always self-limited. An exception is a study that promoted jogging.[51] Little is known about the risk of injury in nonresearch community programs, but injury risk appears controllable.

Because of the high prevalence of arthritis in older adults, the question frequently arises as to whether exercise makes arthritis worse. As shown by consensus guidelines that recommend exercise and physical activity for patients with knee osteoarthritis,[52] the existing evidence strongly favors the conclusion that exercise benefits patients with osteoarthritis. A large study found that strength and endurance training had similar benefit when compared with a control condition.[53] A recent randomized trial in rheumatoid arthritis addressed whether to decrease the exercise load because of arthritis pain. Subjects who did not reduce the exercise load had similar improvements and symptoms as subjects who did reduce the exercise load.[54]

Growth Hormone, Muscle, and Mobility

The initial enthusiasm caused by the report that growth hormone supplementation increased lean body mass has waned.[8] Administering growth hormone subcutaneously can cause side effects such as carpal tunnel syndrome and glucose intolerance.[55,56] Studies have failed to find an effect of growth hormone use on strength, either by itself or in combination with strength training.[56–58] One study reported that growth hormone supplementation has no effect on mobility and functional limitations.[57] Ongoing studies are addressing whether drugs that stimulate the endogenous release of growth hormone from the pituitary gland are useful. These drugs may have fewer side effects and different physiologic effects from those of subcutaneous injections of growth hormone.

Estrogen, Muscle, and Mobility

A possible effect of the use of estrogen on muscle and mobility is only one of many factors affecting the decision to provide estrogen to postmenopausal women. Evidence about the effect of hormone replacement therapy on muscle strength is limited and inconsistent. Studies report that the strength of premenopausal women varies during the menstrual cycle.[59,60] An epidemiologic study reported that estrogen use is associated with the preservation of muscle strength in postmenopausal women.[61] Hormone replacement therapy increased isometric back strength in one study,[62] but other studies report no effect of hormone replacement on muscle strength or mobility.[63,64]

Testosterone, Muscle, and Mobility

Supraphysiologic doses of testosterone increase muscle strength by a modest amount (5% to 20%) in young men.[65,66] Testosterone replacement in younger hypogonadal men improves muscular performance also by a modest amount,[67,68] but less information is available on older hypogonadal men.[69] The effects of testosterone on mobility and functional limitations are unclear. Enthusiasm for long-term testosterone replacement is mitigated by a concern about side effects such as cancer. A recent review discusses trophic factor use in older adults in more detail.[70]

Vitamins

Older adults commonly take vitamin tablets. I was unable to locate studies addressing whether vitamin use affects strength in older adults, with one exception. A study reported that vitamin D_3 use did not affect muscular performance.[71]

Public Health Recommendations

The health problems caused by physical inactivity are substantial, and inactivity is second only to tobacco use in causing premature death in the United States.[72] Only 20% to 25% of older adults meet the Centers for Disease Control and Prevention's criteria for sufficient levels of physical activity.[73] Even though it is obvious that strength training could preserve muscular performance in older adults, only 5% to 6% of older men and 1% to 3% of older women report doing activities to increase muscle strength like weight lifting.[73]

Healthy People 2000, the US Preventive Services Task Force, and the recent US Surgeon General's report on physical activity all recommend regular physical activity for older adults.[73–75] In particular, the Surgeon General's report affirmed the accumulating evidence favoring the health benefits of strength training in older adults:

> Recent recommendations from experts also suggest that cardiorespiratory endurance activity should be supplemented with strength-developing exercises at least twice per week for adults, in order to improve musculoskeletal health, maintain independence in performing the activities of daily life, and reduce the risks of falling.

Emerging Interventions and Issues in Preserving Muscle and Mobility

Improved Measurement

Muscle power is more logically related to functional limitations in older adults than the peak force of a mus-

cle. Some data suggest that older adults have a greater reduction in muscle power than suggested by data limited to peak force.[76] Routine measurements of muscle power may improve our understanding of how to preserve the physiologic capacity of muscle with age.

Existing performance measures of mobility in older adults focus on simple tasks like standing, sitting, and turning. More sophisticated measures, which include a greater variety and difficulty of tasks, are being developed.[77] These measures may allow a more precise assessment of the effects of interventions on mobility.

Sarcopenia Research

The age-related loss of skeletal muscle has been called sarcopenia. Whereas inactivity and a few diseases like polio and stroke are obvious causes of sarcopenia, it is possible that other contributory causes exist. Some have suggested that contraction-induced injury contributes to sarcopenia.[78] Others suggest that oxidative stress contributes to its occurrence.[79] Interventions to prevent these contributory causes are possible. For example, caloric restriction that has been demonstrated to prolong life in rodents may also reduce the incidence of sarcopenia due to oxidative stress.[79]

Program Options

Because many older adults prefer home-based exercise or physical activity, options for inexpensive strength training at home are being developed and studied.[45,53,80,81] As might be expected in the developmental phase, some programs show more promising results than others.[53,81]

Psychoactive Drugs

Psychoactive drugs are risk factors for mobility problems and falls. In particular, the use of benzodiazepines impairs balance in older adults[82,83] and increases the prevalence of falls and hip fracture.[28,84,85] Studies that explore the mechanism by which psychoactive drugs increase the risk of falls report an interesting association between drug use and muscle weakness.[85] We could not locate an intervention study in older adults of the effects of benzodiazepines on muscular performance, but studies in young adults report that one-time or short-term use of benzodiazepines reduces muscle power and maximal exercise levels.[86,87] The use of these drugs also is a risk factor for inactivity because older adults who take psychoactive drugs are less active and less adherent in exercise programs.[88] The use, however, of antidepressants is best considered separately from that of other psychoactive drugs, along the lines of the adage of the baby and the bathwater. Their use may improve physical activity levels by reducing psychomotor retardation caused by depressive illness.

Alcohol

Excessive alcohol use can cause an alcoholic myopathy. Studies of persons with alcoholism report a greater-than-normal age-related loss of strength.[89] The effects and the mechanism of the effects of moderate alcohol use on muscular performance are unclear. Interestingly, studies have reported better muscular performance and physical fitness in both old and young women who drink than in those who abstain.[90,91]

Excess Disability

Primary diseases of muscle like muscular dystrophy are unusual. If present, they are diagnosed before old age. An obvious hypothesis is that muscle wasting in older adults with chronic illness is not a direct effect of the illness, is due to inactivity caused by the illness, and therefore causes excess disability that can be prevented by exercise. Muscle atrophy amplifies disability because muscular performance is profoundly affected by inactivity.

We anticipate more studies will address the role of strength training in maintaining muscle performance and mobility in different chronic conditions. To date, the most work has been done in persons with arthritis and those with diabetes mellitus. The role of strength training in other prevalent chronic conditions—heart disease, obstructive lung disease, depression, dementia, and the like—is less well studied. For example, a meta-analysis of exercise and depression reported strength training to have a much larger effect on depressive symptoms than endurance training, though only a few studies of strength training were included in the analysis.[92] A recent study in depressed older adults reported that resistance training was an effective antidepressant and also improved strength, morale, and quality of life.[93]

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SUCCESSFUL AGING

Overcoming Barriers to Successful Aging
Self-Management of Osteoarthritis

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(Holman HR, Lorig KR. Overcoming barriers to successful aging: self-management of osteoarthritis. In: Successful Aging. West J Med 1997; 167:265–268)

Maintaining a full and independent life is the essence of successful aging. In the process of aging, health-related events occur that compromise one's activities or even one's independence. Successful reversal of, or compensation for, those events is a component of successful aging. Osteoarthritis, a prototypic chronic disease, is such an event. Essentially incurable, it compromises comfort, physical function, and sometimes independence. In this article we address the ways in which patients, physicians, and other health professionals, working together, can minimize or prevent the harmful consequences of osteoarthritis.

Chronic disease is the principal health problem confronting persons above the age of 65 years. The average person above that age has two identifiable chronic diseases, the presence of which may or may not have an effect on that patient's life.[1] After age 65, arthritis is the foremost cause of disability[2] and osteoarthritis is the principal form of arthritis. Osteoarthritis does not kill; rather, it causes chronic pain and disability. In the absence of a cure, the therapeutic goal is to minimize the disease and its consequences over time. In many ways the management of osteoarthritis provides a model for the management of chronic diseases in general and for the art of graceful aging in particular.

Osteoarthritis results from the disintegration of intra-articular cartilage and from new bone formation around damaged joints. The cause of these changes is not clearly known. The process can be variable, affecting different joints at different times and fluctuating in both the rate of change and the symptoms that result. Inflammation is not commonly involved. Standard medical management consists of the use of systemic analgesic medications, exercise to maintain joint mobility and related muscle strength, and surgical replacement of badly damaged joints. When inflammation is present, intrarticular corticosteroid medications can be helpful. Overall, such treatment is moderately successful in diminishing symptoms but is rarely curative. In particular, it does not stem the progress of the disease. Therefore, discomfort and disability tend to increase over time, intensifying a patient's search for relief.

In general, conventional medical treatment of osteoarthritis addresses the abnormal biology of the disease but little else. As with most chronic diseases, the abnormalities associated with osteoarthritis are only part of the problem. In addition to symptoms such as pain and limited motion, the disease causes reduced physical capability, compromised work capacity, a restriction of social activities, and heightened emotional distress. Taken together, the disease and its consequences create an illness; the patterns of illness vary from patient to patient and change in the same patient over time. Moreover, the different components of the illness interact with one another, adding to the overall complexity and sometimes severity of the illness. For example, pain, loss of social contact, and diminished income can all create emotional distress, which in turn contributes to reduced physical activity. Similarly, lessened use of affected joints leads to muscle deconditioning and reduced strength, thereby increasing disability. These circumstances are intensified when more than one chronic disease is present. In that situation, biologic

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abnormalities, their consequences, and the adverse effects of treatment often interact, creating even more complex illness patterns.

The appropriate management of osteoarthritis is often more complicated than the mere application of conventional medical treatment. Not only must the immediate effects of abnormalities be addressed, the many other consequences also require attention. This entails knowledge of those consequences, including what corrective action must be taken to minimize or prevent them. In our view, the key to appropriate management is recognizing that the patient is the principal caregiver, sometimes with the help of his or her family. This becomes obvious when we consider the tasks that patients must perform, alone or with the family: using medications properly, changing behavior to improve symptoms or slow disease progression, interpreting and reporting symptoms accurately, adjusting to new social and economic circumstances, coping with emotional consequences, and participating in treatment decisions. It is the responsibility of physicians and other health professionals, and of the health care system in general, to help patients and their families become skilled at these tasks, to reinforce and support their efforts, and to provide the lines of communication and services that facilitate the new behavior pattern. This in turn means creating an effective partnership between the patient and the responsible physician, one in which each bears clearly identified responsibilities for the management program.[3]

The skills vital to the central role of patients in the care of osteoarthritis may be summarized as follows:

- *Using medications properly*

The proper use of medication requires understanding the medication, its purpose, benefits, and possible adverse side effects; finding easy ways to remember when to take medications; and having prompt access to advice when problems arise. In the management of osteoarthritis, the purpose of medications is to control pain, not to suppress inflammation. Acetaminophen has been shown to be as effective in this regard as more expensive analgesic and antiinflammatory drugs. In the management of chronic arthritis, nearly 50% of patients do not fully comply with medication regimens.[4,5] Although noncompliance may be attributable to the ineffectiveness of the medicine, poor understanding, a lack of accessible advice, or an unsatisfactory relationship with the physician are also known to be contributing factors.

- *Changing behavior to improve symptoms or slow progression of the illness*

For a patient with osteoarthritis, many other behaviors in addition to proper medication use may be helpful. For example, pain can often be relieved by using relaxation or cognitive distraction techniques, or even heat or cold to the painful area.[6] Also, regular exercise of affected joints, especially endurance exercise, not only retains mobility but counteracts the loss of muscle strength from disuse.[7,8] Illness progression is often as much created by loss of mobility and strength from disuse as it is by the arthritic process itself. Thus, progression can be limited by appropriate exercise. Similarly, persistence in social activity despite handicap or deformity will minimize depression, which by itself can intensify the seriousness of an illness.

- *Interpreting and reporting symptoms accurately*

Patients with osteoarthritis need to interpret and report their symptoms accurately. This is important for two reasons. First, only the patient knows accurately the full effects of the disease and its treatment. Reporting symptoms and side effects to health professionals is critical to the design and midcourse correction of treatment programs. Thus, patients need to acquire skill in recognizing and describing symptoms. Second, accurately interpreting symptoms is central to effective self-management. For example, if pain is interpreted as indicating disease progression, the patient will tend to avoid activities that increase pain. If, on the other hand, the pain is interpreted as stemming from an effect of the disease such as deconditioning, then for therapeutic reasons the patient should increase activity, especially exercise. Similarly, if physical weakness is interpreted as a consequence of disease that is responsive to medication, medication will tend to be increased; if it is seen as a consequence of deconditioning, exercise would be the appropriate therapeutic measure. In addition, medications have potential adverse effects, some of which mimic symptoms of arthritis. Accurate discrimination of symptoms allows appropriate responses. Such reframing of symptom interpretation is central to selecting suitable strategies of both management and professional treatment.

- *Adjusting to new social and economic circumstances*

Discomfort and disability can restrict a person's social life and work capacity, leading to increased isolation. The maintenance of normal activities is a primary goal of successful aging. Reorganization of the time, place, context and duration of social contacts can minimize the handicapping effects of osteoarthritis. Similarly, adjustments in working conditions, such as the use of assistive devices and sheltered workplaces can be of substantial aid in maintaining a person's productivity.

- *Coping with the emotional consequences of osteoarthritis*

Worry, frustration, anxiety, and situational depression are common accompaniments of physical discomfort and handicap. It is crucial that patients perceive them as symptoms of the underlying disease and its consequences and not as personal failings. Recognizing negative emotions as symptoms allows patients to address their condition in practical terms. They can do this in the following ways: by encouraging greater tolerance and understanding, by themselves and their families; by

seeking to improve their situation through self-management activities; by forming new social or work habits and connections (for example, joining a support group); and by the appropriate use of medications.

- *Use of community resources*

Many communities offer programs of value to persons with osteoarthritis. These include organized exercise programs, swimming facilities, information meetings, social activities, self-help education, support groups, and mobile services for transportation and meals. The Arthritis Foundation and its chapters are a ready source of information about such activities and services.

- *Developing a partnership with the physician and other health professionals*

The foundation of effective management of chronic arthritis is the development of a partnership between patients and health care professionals. Patients know best the effects of the disease and its treatment, how well self-management practices are working, and what they hope to achieve in the future. The physician and other health professionals, on the other hand, know best the general methods for managing osteoarthritis, the available self-management methods and the strengths and weaknesses of different medical or surgical approaches. All those involved in this partnership, both patients and health care professionals, can contribute knowledge of community resources. Integration of this knowledge leads to the most appropriate management program.

How can the patient's role be achieved? There are three realms where action by the health care system is necessary. The first is developing and installing patient education programs which impart both the knowledge and the skills for self-management and for partnership with health professionals. The second is achieving new behaviors by physicians and other health professionals that support patient education, that reinforce and sustain self-management practices, and that create an environment that enables a partnership to emerge and grow. The third is reorganization of health services to provide the patient education, to support physicians and other providers in their new responsibilities, to facilitate easy communication between patients and health care providers, and to reorganize finances to support the new services.

Substantial evidence is available concerning the benefits of patient education in the management of osteoarthritis and other forms of chronic arthritis. A meta-analysis of previous studies was published in 1987.[9] Additional studies have assessed the value of different self-management forms.[10–14] In our own studies, participation by patients with osteoarthritis in the Arthritis Self-Management Program (ASMP) led to substantial declines in pain and depression, as well as a reduction in the use of health services.[10] Four years after participating in ASMP, without follow-up reinforcement, patients continued to report major reductions in pain and in the use of health services despite a 9% increase in measured physical disability.[15] The cumulative evidence for the benefits of self-management in cases of osteoarthritis, coupled with similar evidence for its effectiveness in treating chronic diseases in general, leaves little doubt that this approach provides a valuable supplement to current health care practices.

It is unclear precisely how self-management practices achieve their advantageous results. Following a training program, knowledge grows and patient behaviors change in many ways. We have found, however, that although patient behavior changed considerably, these changes correlated only weakly with the benefits achieved.[16] A much stronger correlation has been found with the patients' perceived ability to cope with the consequences of their arthritis.[17] That is, as a result of training, their confidence in their abilities grew. Interestingly, it emerged from the four-year study that as time went on, patients' confidence continued to grow. This may well explain their sustained reductions in pain as well as their reduced need for medical services.[15] Based on the combined results of the aforementioned studies, it is reasonable to assume that the various effects of training, which include growth in knowledge, the acquisition of specific self-management behaviors, and changes in attitude, all contribute to the beneficial outcomes.

Will the average patient be interested in learning and practicing self-management? This is an important questions for at least two reasons. First, the studies of self-management have been experimental in nature and conducted only in volunteers. Although volunteers have been numerous and participation has been substantial when similar programs have been offered by the National Arthritis Foundation, it is difficult to predict the extent of participation should self-management training be offered to all patients as a routine component of health care service. Second, most of the studies were conducted outside of standard health care institutions. If self-management training can be incorporated into the health care system, with support of the physicians, its appeal may be significantly enhanced. Interest will doubtless vary among patients, but there is reason to expect that it will be substantial. For example, we have recently completed focus group discussions with some of our primary care patients suffering from chronic diseases, the purpose of which was to elicit information about their wishes regarding medical care. Consistently and strongly, these patients identified the following as their most urgent needs: information about the disease and its implications for their lives, easy communication with health professionals, the acquisition of self-management capabilities, and the opportunity to learn from other patients. To give a further example, when participants in the ASMP were asked which components of the program they found most valuable, the most common answers were, first, the opportunity to learn from other patients and, second, the chance to help other patients.[18] Recently the Kaiser health plan in Colorado

instituted group visits by patients with their physicians and other health professionals in which the patients set the agenda. Both patients and physicians have rated these test visits as extremely useful and have asked that they be continued.[19] Finally, when physicians who involved patients in decision making were compared with physicians who did not, it was found that patients expressed significantly greater satisfaction with, and were more likely to continue seeing, the former.[20]

What can we expect from our health care system once it has been changed along the lines we are advocating? The clinical and experimental evidence is clear. Assuming that the results can be transposed to a general setting, the outcomes should be as follows:

- Patients will report fewer symptoms, less emotional distress, increased activity, and more independent living.
- There will be decreases in the direct and indirect costs of health care for osteoarthritis in particular and for chronic diseases in general. For example, cost-effectiveness analyses that have been conducted in some of the aforementioned studies on patient self-management education have indicated that the savings in overall health care costs may be eight times greater than the cost of education. As crude as these analyses have been, they do suggest that we can expect substantial savings from the widespread use of self-management practices.
- Both patients and health professionals will report higher levels of satisfaction.

In many ways, the concepts and practices discussed in this article will seem self-evident both to patients with chronic arthritis and to experienced clinicians. But they are not commonplace in contemporary health care. The reasons for the disparity between health care needs and what the health care system currently provides are beyond the scope of this paper. The problem has partly to do with the origin of the health care system at the turn of the last century—at a time, that is, when acute diseases predominated. In that setting, patients were inexperienced and passive; physicians were possessed of all the available knowledge and skill and consequently determined the course of action.[21,22] The problem lies also in the advantages that have accrued to the profession owing to its socioeconomic dominant position.[23] At about the middle of this century, however, matters changed. Chronic diseases replaced acute diseases as the most prevalent cause of medical distress. At the same time, the population of older persons (who disproportionately experience chronic disease) began to increase. Both of these trends have continued steadily. Today the contradiction between a health care system built for acute disease and the chronic health problems that people more commonly have is vividly reflected in the fact that the treatment of chronic disease is responsible for 70% of current health care expenditures.[24]

The urgent need today is to make health care services commensurate with existing health problems. Doing so entails creating new roles for patients, health professionals, and the health care system overall. The starting point for health care reform is to forge partnerships between patients and health professionals. It is the responsibility of the health care system to foster and serve that partnership. Seen from the larger perspective of our country's health care system and the medical needs of its population, the appropriate care of osteoarthritis is a perfect example of both what is not and what needs to be.

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SUCCESSFUL AGING

Memory, Thinking, and Aging
What We Know About What We Know

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Cognition is the foundation that underlies all daily activities, from the most basic to the most complex. Successful aging depends, in large part, on maintaining a level of cognitive ability that allows a person to interact effectively and appropriately with the environment. In the following article we provide an overview of the effects of aging on cognition; discuss physical, social, and psychological factors that have been shown to influence cognition in old age; and review current literature on interventions that may optimize successful cognitive aging. We conclude with a discussion of abnormal cognitive aging and review current research on risk factors and treatments of Alzheimer's disease and other dementing illnesses.

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Every action of every day is mediated and influenced by our cognitive abilities. From the most sophisticated human activity to the most mundane, everything we do depends on our capacity to understand and interact with our environment. Our ability to interact with those around us, converse, successfully solve daily problems, and even dress, bathe, toilet, and feed ourselves all depend on our level of cognitive function. Consequently, successful cognitive aging is an essential substratum of successful aging.

Cognitive health does not exist in isolation. Quite the contrary, it influences, and is influenced by, an array of medical, social, affective, and functional changes that often occur with increased age. For example, it is well known that a host of medical diseases and medications can adversely influence cognitive abilities in older adults. Conversely, impaired cognition may cause older adults to misunderstand their physicians' instructions, to take their medications improperly, and to have generally more difficulty complying with preventive and secondary health regimens.

Rather than being unidimensional, cognitive health is multidimensional. It encompasses an array of functions, including general intellectual ability, memory, language, visual-spatial skills, perception, and complex problem solving. Each of these areas represents complex domains. For example, the term "memory" refers to a diverse array of activities, including the abilities to remember past events (remote memory), learn new information (recent memory), remember future events (prospective memory), perform familiar activities (procedural memory), and learn without directed effort (incidental memory).

Consequently, successful cognitive aging must be defined in such a way as to take into account the interactive and multifaceted nature of cognitive function. Several definitions have been proposed to attempt to capture the concept of successful cognitive aging. Some have defined "successful" as the upper strata of cognitive functioning.[1,2] According to these authors, only those persons who score substantially above the mean (defined in various ways) are aging successfully. Others have defined "successful" as having minimal interruption of usual function.[3–7] This latter definition reflects a more interactional approach and suggests that success reflects the extent to which a person is able to interact effectively with the environment and adapt to age-related changes.

In this article, we will adhere to this multifaceted and interactive definition: successful cognitive aging is the

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ABBREVIATIONS USED IN TEXT

EPESE = Established Population for the Epidemiologic Study of the Elderly
SLS = Seattle Longitudinal Study

interplay between cognitive status and a person's ability to adapt, accommodate, and adjust to the environment. In so doing, we think we provide a definition of the most direct relevance to older adults and their health care practitioners. We will survey the cognitive-aging literature, beginning with an overview of what is known about the areas of cognition likely to be affected by increasing age and those unlikely to be affected. We will then discuss the factors known to influence cognitive functioning in old age, concentrating on three areas that are the primary focus of current empiric research on successful aging, namely, physical, social, and psychological health. Once we understand what areas of cognition are affected by age and what mediates those effects, the next logical step is to identify what can be done to optimize successful cognitive aging. To answer this question, we turn to the intervention literature. By far, most intervention research has emphasized memory training, so we will focus primarily on the use of such strategies with older adults.

Finally, considering the factors that might enhance successful aging and mitigate decline naturally leads to a discussion of the dementing disorders of late life because they represent the opposite end of the cognitive aging spectrum. By understanding risk factors for these diseases, we might better understand how to prevent these disorders, ensure optimal function, or both. By understanding what cognitive-enhancing strategies have been investigated in dementia, we may discover useful techniques for improving cognition in nondemented older adults. We will conclude by suggesting directions for future research and avenues of clinical treatment.

Cognitive Changes With Normal Aging

Considerable research has been done on the changes in cognition that are associated with aging. Early work conceptualized general human intellect as having two aspects: crystallized intelligence, which includes overlearned, familiar skills accumulated through education and practice, and fluid intelligence, which includes nonverbal reasoning, motor tasks, and problem-solving abilities that evolve and change as a result of physiologic maturation.[8,9] It was theorized that crystallized abilities—such as knowledge of general facts and vocabulary—sharply increase during the early years of formal education and then stabilize or gradually improve throughout adulthood. In contrast, fluid abilities improve throughout childhood, then gradually decline in adult years, with more rapid deterioration in old age due to neuronal loss, changes in physiologic brain function, and increased rates of disease and injury. This general intelligence approach has been criticized by adherents of more complex cognitive theories, who say that intellect is a function of many distinct factors that decline at differential rates and that should be considered separately in the evaluation of normal cognitive aging.[10] Others have argued that psychomotor or cognitive slowing can explain most if not all of the measured changes in performance that are associated with aging.[11]

Despite this controversy, both cross-sectional and longitudinal studies have supported the relative stability of verbal abilities with advancing age and the decline in tasks requiring perceptual speed, selective attention, and complex problem solving.[12–14] The largest and most extensively documented study of cognitive changes associated with normal aging is the Seattle Longitudinal Study (SLS),[6,15] which has been observing multiple cohorts of aging adults since 1956. More than 3,000 cognitively intact subjects have been enrolled and evaluated every seven years in five cognitive domains: verbal meaning (recognition vocabulary), spatial orientation (ability to rotate objects mentally in two-dimensional space), inductive reasoning (ability to generate novel concepts or relationships), number skills (simple addition), and word fluency (verbal recent memory and word-list generation from lexical categories). The SLS has shown that performance on all cognitive domains begins to decline by age 74, although this is mediated by gender and cohort effects. Specifically, women decline earlier on fluid abilities, whereas men decline sooner on measures of crystallized ability.[16] Cohort differences have also been observed in patterns of decline: subsequent generations have showed steady improvement in inductive reasoning, verbal meaning, and spatial orientation during the SLS sampling period, in contrast to declining number skills and, to a lesser extent, declining verbal memory and fluency.[16]

Considerable consensus exists that important interindividual differences explain age-related cognitive decline.[17–20] In the SLS, few subjects have shown global decline; rather, most participants maintained or increased their level of performance on at least one cognitive domain well beyond 80 years of age, suggesting that successful cognitive aging involves selectively maintaining abilities.[21] When decline does occur, the age of the start of decline varies widely. The reasons for this variation are largely unknown; researchers have suggested that differences between subjects may be due to such factors as genetic predisposition, chronic disease, socioeconomic differences, level of intellectual and environmental stimulation, and personality.[6,10,19,22]

Some authors have distinguished between cognitive ability and cognitive competence. The term "competence" is not used here to imply legal capacity for decision making. Rather, it refers to a person's potential to use a combination of personal resources, including past experience, physical and interpersonal skills, and cognitive abilities, to adapt to particular situations.[23] It helps explain why some older adults who score low on neuropsychological tests of complex problem-solving tasks nevertheless remain capable in highly demanding occu-

pations, avocational pursuits, or challenging personal circumstances. Cognitive competence is a useful construct because of its implications for successful aging and remediation. For example, continued late-life involvement in productive activity has been associated with higher levels of physical and cognitive functioning.[24] Cognitively competent older adults who desire to remain productive in paid or volunteer activities may be able to draw on previous experience and interpersonal skills to offset circumscribed age-associated cognitive decline.[25] Even older adults with substantial physical or cognitive limitations can capably pursue personal goals in their own environment when they are allowed access to external aids, social supports, or technologic advances to compensate for age-related losses.

Correlates of Successful Cognitive Aging

In the past ten years, several large multivariate epidemiologic investigations have been conducted in various parts of the United States to identify what factors contribute to the maintenance of cognitive and functional abilities with advancing age.[2,6,17,21,26,27] These studies have focused on three main research areas, namely, the role of physical, social, and psychological health in the maintenance of cognitive function. Although each investigation has defined successful cognitive functioning in a different way and each has assessed different factors that are proposed to be related to cognition, some common themes have emerged.

The first theme has already been described. Persons vary widely in the type and severity of cognitive changes shown with advancing age. For example, in the SLS, few showed global decline; rather, most maintained or improved their level of performance in at least one cognitive domain well beyond 80 years of age.[21] When decline did occur, the age of the start of decline varied widely. Similarly, in the Georgia Centenarian Study, which investigated variables related to cognitive functioning of 165 participants aged 60 to 100,[27] overall intellectual functioning was lower in the oldest cohort, but everyday problem solving remained intact even among the oldest subjects.

Despite this variation, consistent mitigating factors have been identified and replicated across different studies. Educational achievement has been found to be a strong predictor of cognitive functioning in later decades of life. Persons with higher educational levels show less age-related decline.[1,19,22,26,28,29] Educational experiences early in life also appear to exert some protection against the cognitive deterioration associated with dementing illnesses.[30] The SLS found that education was significantly correlated with the maintenance of certain aspects of cognitive function, particularly in the areas of verbal meaning and fluency and inductive reasoning.

Physical health status, including number of illness episodes, chronic disease, exercise participation, and subjective reports of health and health-related activities, such as alcohol and tobacco use, have been consistently correlated with cognitive function in older adults.[1,2,17,26,31] For example, in the SLS, cardiovascular disease was the primary health-related variable predicting cognitive decline.[31] Persons with cognitive decline averaged ten times as many hospital admissions for cardiovascular disease as those without decline and had twice as many cardiovascular-related outpatient medical visits. All subjects in this investigation belong to the same health maintenance organization (Group Health Cooperative, Seattle, Washington), which maintains a uniform health care database on all its members. Thus, this investigation provided a unique, objective assessment of health changes in its study participants.

Possibly modifiable health factors including strenuous physical activity, pulmonary function, and cardiovascular status have also been identified as important factors in the maintenance of cognitive ability. For example, another longitudinal study, the Established Population for the Epidemiologic Study of the Elderly (EPESE)–MacArthur Foundation Research Network, evaluated a sample of 4,030 persons aged 70 to 79 years from which 1,192 subjects were identified as "high functioning," based on brief assessments of physical and cognitive status.[26] These subjects were compared with age- and sex-matched subjects who were in the "medium" or "low-functioning" groups. High-functioning subjects rated their health much higher, smoked fewer cigarettes, exercised more, and had better pulmonary function than medium or low-functioning subjects.

Emotional state has been found correlated with cognitive function in late life. Self-efficacy (the belief that through one's actions, a person can produce a desired effect), depression, and anxiety have each been significantly associated with cognition. For example, in the EPESE study, the high-functioning elders scored higher on scales of self-efficacy and mastery and reported fewer symptoms of anxiety and depression than lower functioning elders.[26] In EPESE subjects, lower self-efficacy was significantly predictive of greater cognitive decline over a $2\,^1/_2$ year period.[1] Mental health was also significantly related to cognitive ability in the Georgia Centenarian Study,[27] in that persons who had higher cognitive ability had lower levels of depression and anxiety.

In summary, age-related cognitive decline is variable, but factors influencing decline have been identified and replicated across the different groups studied. Previous educational achievement was consistently one of the strongest predictors of cognitive functioning in the later decades of life, with more education mitigating decline in late life. Physical status has been consistently correlated with cognitive function, including such potentially modifiable factors as strenuous physical activity, pulmonary function, and cardiovascular health. Emotional health variables were also important factors in the alteration of cognition with increasing age; symptoms of depression and anxiety were consistently associated with lower cognitive functioning, whereas self-efficacy was strongly predictive of better cognitive functioning.

Interventions to Enhance Successful Aging

Memory Training Trials With Normal Older Adults

In recent years, evidence has been growing that training or practice can reverse some aspects of age-related cognitive decline or improve performance in persons who have been relatively stable but are disadvantaged relative to younger peers.[6,22,32] Of particular relevance to normal older adults are training programs for age-associated changes in memory.

Memory loss is widely considered the hallmark of age-related decline in our culture and is one of the most common complaints of older persons. Controlled intervention studies generally include instruction in one or more mnemonic techniques to improve memory performance. Most mnemonic techniques involve using mental imagery to create a visual memory cue; for example, in the "method of loci" approach, subjects are asked to imagine a room in their home and to mentally place items from a grocery list at sites around the room. The grocery list items are thus paired with the familiar objects in the room, and this visual paired association enhances list recall. Many memory training programs also include a "pretraining" component, such as relaxation training or teaching semantic elaboration skills to help subjects form associations between a name and a prominent physical characteristic. Pretraining precedes actual mnemonic instruction and is intended to increase participants' treatment gains by providing them with basic skills needed to perform the mnemonic techniques successfully.

A number of studies have shown that memory training can improve memory performance in older persons. Verhaeghen and co-workers reviewed 31 studies in which 1,539 healthy older adults (mean age 60+ years) were taught mnemonic techniques to improve memory performance.[33] A meta-analysis of treatment gains found that treatment gains were larger in mnemonic training groups than in either control or placebo group comparisons. Change scores were also greater when training was conducted in a group (versus individual) format, when pretraining or additional memory-related interventions (such as education on using external memory aids or motivation enhancement) were provided, when subjects were younger, and when sessions were relatively short. Improvement was also greater when the post-treatment outcome was measured with tasks that matched the training condition (for example, a name-face recall task following training in mnemonics for associating names and faces). There were no significant differences in treatment gains with the type or number of mnemonic techniques taught, type of pretraining, number of training sessions, or the presence of an actual trainer (as opposed to getting information from a manual or tape). These findings indicate that older adults can improve their episodic memory, which has implications for some areas of memory function that are important to successful aging, such as remembering important dates, appointments, and phone numbers or recalling names of family and friends.

Stigsdotter and colleagues have examined the long-term maintenance and generalizability of memory training effects.[34–37] The delayed effects of training were assessed in several studies that observed a total of 42 older adults. In the first, 18 subjects were randomly assigned to one of three conditions: a multifactorial memory training program (that included training in visual imagery, relaxation, and divided-attention tasks), a cognitive activation program (with problem-solving and visual-spatial skills training), or a control group.[34] After testing and at six-months assessment, only the subjects in the multifactorial memory training program had substantially improved over baseline on a selective test of reminding word-list recall. In the second study, 24 subjects were assigned to either a multifactorial training program, a unifactorial training group (mnemonic imagery training but no attention or relaxation training), or a control condition.[35] Subjects in both the multifactorial and unifactorial groups scored better after testing and at six months than did subjects from the control group, suggesting that the mnemonic training component, not attention or relaxation training, is the active memory-enhancement ingredient.

When subjects from both studies were subsequently retested 3 1/2 years later, all groups scored at the same level as they had at the assessment six months after treatment, indicating the prolonged effect of training.[36] Mean scores for the active treatment groups (the multifactorial and unifactorial memory training groups) were significantly higher at the 3 1/2-year follow-up than they had been at pretraining baseline. No improvements were found for subjects in either control group. The combined results from these three studies suggest that memory training can produce long-term effects for older adults, at least for memory tasks that are congruent with the training activity. In a subsequent study with 46 older subjects, the same authors repeated their findings by showing significantly improved and sustained treatment effects for participants in a multifactorial training group compared with controls.[37] Improvements were found only for the recall of nouns and concrete objects, however; memory tasks unrelated to the mnemonic (visual imagery) training, such as remembering abstract words or personal activities, were not improved with training. In fact, the authors speculated that training may actually have interfered with subjects' recall on unrelated tasks.

In sum, these studies suggest that older adults can improve their memory performance with training, although the apparent benefit declines with advancing age. Training is most effective for episodic memory tasks that match the training condition. Because there is little evidence that training gains transfer readily to other, untrained memory activities, many of the most important memory tasks of older persons (such as prospective memory for future appointments) may not be affected by traditional memory training approaches. The literature has also provided evidence for the value of memory pretraining and memory-related interventions. The value of these may lie in their effect on older

adults' beliefs about the modifiability of late-life memory skills[38,39] and on the enhanced sense of control and competence that arises from learning mnemonic skills or effectively using external memory aids.[40,41]

Lifestyle Changes to Improve Cognition in Normal Older Adults

Based on the review presented earlier, it appears that education, self-efficacy, and physical and psychological health may facilitate or maintain higher cognitive functioning. Conversely, higher cognitive function may facilitate better physical and psychological health. In an early review of normal and successful aging, it was speculated that many of the cognitive losses associated with aging are caused by extrinsic factors (nutrition or personal habits) and are therefore preventable.[42] Consequently, treatments designed to improve self-efficacy, lessen depression and anxiety, and facilitate lifelong learning may well have a beneficial effect on cognitive health.

An area of lifestyle change that deserves particular mention is the current interest in the effects of estrogen levels on cognition in older women and whether estrogen replacement therapy may slow or reverse normal age-related decline. Recent reviews of estrogen supplementation and cognition have found evidence for a positive relationship between estrogen use and verbal memory, concept formation, and reasoning.[43,44] Although these findings have therapeutic implications for successful aging, the demonstrated treatment effects of estrogen on cognition have been modest, raising questions about the relative clinical benefits versus possible medical risks. Only a few studies have looked at the possible long-term effects of estrogen on cognitive function; a greater number have examined the possible secondary influence of estrogen on cognition through its mood-enhancing effects, but study findings have frequently been equivocal and contradictory.[43,44] In sum, although estrogen therapy appears to have some promising benefits for maintaining cognitive ability, the literature at present remains investigational, and it would be premature to conclude that estrogen supplements should be routinely prescribed to normal older women for its cognitive-enhancing effects.

Risk Factors for Cognitive Impairment

At the opposite end of the spectrum from successful cognitive aging is the cognitive decline associated with dementing illnesses. The hallmark of dementia is progressive memory loss. Memory loss alone is not sufficient to warrant a diagnosis of dementia, however. Rather, it must be accompanied by other changes in cognition severe enough to interfere substantially with daily functioning, including impairments in judgment, language, motor dexterity, or disturbances of higher executive function such as planning or abstract reasoning.

It is estimated that almost 2 million older adults in this country have severe dementia, and another 1 to 5 million have mild to moderate dementia.[45] The most common types of progressive late-life dementia are Alzheimer's disease and vascular dementia, which account for more than 75% of the cases of dementia diagnosed in the United States.[46,47] Other common types include subcortical dementias such as Parkinson's disease or Lewy body diseases, frontal lobe dementia, and dementia resulting from prolonged alcohol abuse.

Just as there are numerous medical causes for the common forms of dementia, so, too, are there various risk factors for their development. For example, the risk factors for vascular dementias are the same as those for vascular disease and stroke, such as hypertension, obesity, diabetes mellitus, hypercholesterolemia, smoking, and lack of exercise. Alzheimer's disease, although less well understood etiologically, is strongly associated with increased age, and there is growing evidence for both genetic and environmental contributing factors. Characterized as an irreversible, degenerative disease with insidious onset and gradually progressive course, Alzheimer's disease affects about 5% of adults older than 65 and between 20% and 50% of persons older than 80.[45] Age, however, is neither necessary nor sufficient for the development of Alzheimer's disease. A number of cases of the disease have been reported with onset in young or middle adulthood, and many persons age well into their 80s and 90s without having any signs of dementia.

What then, may differentiate older adults at risk for dementia from those not at risk? Besides age, family history is probably the clearest risk factor for Alzheimer's disease. Genetic studies have led to the identification of gene mutations on chromosomes 1, 14, 19, and 21 that are strongly implicated in familial forms of Alzheimer's disease,[48,49] including β-amyloid precursor protein, presenilin-1, presenilin-2, and the ε-4 allele of apolipoprotein E (*APOE-E4*). In fact, recent studies have suggested that increased risk is dose dependent and that the *APOE E4/4* genotype may be associated with an increased risk for accelerated cognitive decline.[50]

In addition, Alzheimer's disease does not necessarily occur alone. Several recent studies have linked the risk factors for Alzheimer's disease to other diseases. For example, *APOE E4*, the genetic marker discussed earlier, has also been implicated in coronary artery disease. Vascular disease and Alzheimer's disease can coexist: subjects with documented lacunar infarcts (strokes) are at an increased risk for Alzheimer's disease. In addition, diabetes mellitus has been found to increase the risk of dementia threefold.[51]

Environmental risk factors for dementia have also been identified, although not as consistently as the genetic markers. Two of these, antioxidants and estrogen, have received particular attention because of their apparent protective effects for Alzheimer's disease. Vitamin E, an antioxidant, has been implicated in a variety of chronic diseases associated with cognitive decline, such as ischemic heart disease, atherosclerosis, diabetes mellitus, and peripheral neuropathies. Although the role of vitamin E in the development of Alzheimer's

disease is still unclear, a recent controlled clinical trial has shown that the use of vitamin E alone (and in conjunction with selegiline hydrochloride [Eldepryl]) can slow the progression of Alzheimer's disease.[52,53] Estrogen is thought to have several mechanisms of action in the brain, including facilitating anticholinergic activity and the growth of cholinergic neurons, enhancing glucose use by brain cells, and maintaining brain cell. Estrogen has also been linked to emotional state, which in turn affects cognitive function.[43] Thus, the role of estrogen in cognitive aging is still unsettled, but it is likely to be multifactorial and important.

Treatments

By far the most successful treatment of dementia occurs when it is determined that cognitive decline is caused by an underlying reversible disorder that can be treated. Hypothyroidism and vitamin B_{12} deficiency are two of the most common reversible causes found in older adults.[47] Unfortunately, the most common dementias in elderly persons are the "irreversible" types, dementias with no known cause, such as Alzheimer's disease, or those with causes of limited treatment potential, such as vascular disease.

Because no clear "cause" for Alzheimer's disease has yet been identified, treatment has focused on ameliorating the symptoms, both cognitive and otherwise. Thus far, two "cognitive enhancers" have been approved by the Food and Drug Administration for the treatment of Alzheimer's disease and are currently available: tacrine hydrochloride (Cognex, Parke-Davis) and donepezil (Aricept, Pfizer). Both drugs block the breakdown of acetylcholine, the neurochemical consistently deficient with neurodegenerative cell loss. As noted earlier, selegiline and vitamin E have also been investigated in the treatment of Alzheimer's disease and found to slow the progression of the disease over the course of two years.[53] It is also worthwhile to note that a growing body of literature has suggested that both pharmacologic and nonpharmacologic approaches can be effective in reducing the neuropsychiatric and behavioral sequelae of Alzheimer's disease,[54,55] and this may also have implications for improved cognitive function in some affected persons.

Summary and Conclusion

Successful cognitive aging is essential to successful aging as a whole. Numerous definitions have been proposed to describe adequately this important phenomenon. We have followed those that take into account the interactive and multidimensional nature of cognition. Successful cognitive aging is defined as the extent to which a person is able to interact effectively with the environment (both interpersonal and physical) and adapt to age-related changes. Successful older adults, therefore, are the ones who have a minimal interruption of their usual level of function.

Considerable research has been done on the changes in cognition that are associated with aging. Cognition is not unidimensional. Rather, it includes a wide array of verbal and nonverbal skills, including general intellectual ability, memory, language, visual-spatial skills, perception, and complex problem solving. Both cross-sectional and longitudinal studies have supported the relative stability of verbal abilities with advancing age and the decline in nonverbal tasks, particularly those involving speed of response. Within this generalization, however, and given the great variation of skills encompassed in the term "cognition," it is not surprising that sizable intraindividual and interindividual differences occur across the age span. Few persons show global decline. Selective maintenance of abilities seems to be the rule rather than the exception.

Several large multivariate epidemiologic studies have consistently implicated the following variables as mitigating factors in the change of cognitive skills with advancing age:

- Educational level;
- Physical health status, including comorbid medical disease and physical activity; and
- Emotional health status, including depression, anxiety, and perceived self-efficacy.

Randomized controlled clinical trials to enhance successful cognitive aging have focused on age-associated changes in memory. Interventions generally include instruction in one or more mnemonic techniques, and such instruction has been effective in producing targeted, short-term gains. Observed benefits tend to decline with advancing age, however, and whether such gains have functional generalizability remains unknown.

When substantial decline in cognitive abilities occurs, as in the case of the dementing disorders, the causes of such decline are largely unknown. Age is the single strongest predictor of dementia, although age alone is insufficient to predict cognitive decline. A genetic predisposition to decline is the second strongest predictor. Environmental risk factors are also currently being investigated, with particular attention to dietary and hormonal supplements.

We clearly know more now about successful and unsuccessful cognitive aging than we did a scant five years ago, but we have a long way to go. Unanswered questions remain. The best help to our patients is to provide them with our knowledge: some will age successfully, and some will not. For the former, mnemonic training programs offer some hope; for the latter, medications such as tacrine and donepezil and behavioral programs offer respite. In the long run, however, more research is needed to understand how best to predict and enhance successful cognitive aging.

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SUCCESSFUL AGING

Maintaining Good Morale in Old Age

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Traditional aging studies have seen life's later years as a time of inevitable biological and social decline. Psychological decline might also be expected, but this is not true for most older people, according to epidemiologic studies. Thus, we must ask: Why is aging not as emotionally threatening as might be expected? Why do some older people do better than others? How should medicine address these issues? It is only possible to understand the successful emotional aging of most elders if the customary diathesis-stress model is supplemented by a developmental perspective. Expectations as well as capacities diminish with aging. This means that subjective health appears more tightly linked with morale than objective health. Some older people experience recurrence of mental disorders (for example, major depression) first present earlier in life. Others experience new disorders such as minor depression in response to biological or social losses. As geriatric medicine comes to increasingly focus on chronic disease, attention to morale is an important strategy for maximizing quality of life. Physicians will need improved skills in the detection and treatment of problems in morale if they are to provide optimum care for their older patients.

(Sullivan MD. Maintaining good morale in old age. In: Successful Aging. West J Med 1997; 167:276–284)

You see me here, you gods, a poor old man,
As full of grief as age; wretched in both!
WILLIAM SHAKESPEARE
King Lear

Since its inception, the study of aging has been dominated by the metaphor of a hill: gain in childhood, adolescence, and young adulthood, followed by decline in middle and old age. Aging persons face not only the acceleration of death rates with age—which Gompertz called the "force of mortality"[1]—but a decline in measurable cognitive and perceptual abilities, such as Galton's "reaction time." There is also an increasing burden of symptoms and disability from chronic illness. Important relationships are also lost as spouse, friends, and family die. Given these progressive and largely irreversible losses, it is surprising that most elders do not slip slowly into despair.

Therefore, we must ask why, in the face of progressively worsening biologic and social circumstances, most elders do not experience substantial affective decline. Four possible explanations for this psychological hardiness have been proposed[2]:

- Chronic illness can offer social advantages in the form of increased involvement, concern, and attention from important others;
- Older persons may have better developed skills to cope with adverse life events;
- The perspective of an older person may promote better adaptation to chronic illness;
- Older persons may have better biologic capacity to adapt to chronic illness.

Although all of these factors may play a role in successful emotional aging, the following evidence will point most heavily to the third option: changes in perspective allow an adaptation to changes in circumstances.

How are we to understand this changing perspective? Diathesis-stress models are the most commonly used theories to explain the onset of mental disorders. In these models, a diathesis (trait vulnerabilities, including but not limited to, genetic factors) interacts with stress to produce a mental disorder. A diathesis may lead to a disorder only in the presence of adequate stress. Similarly, a person who does not carry the diathesis may not have

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ABBREVIATIONS USED IN TEXT

ECA = Epidemiologic Catchment Area
EPESE = Established Populations for the Epidemiologic Study of the Elderly
HMO = health maintenance organization
MRI = magnetic resonance imaging

a disorder even in the face of severe stress. Most diathesis-stress models, however, do not take a developmental perspective. There is little understanding of how the diathesis for mental disorders changes during the life cycle. If we do take this perspective, we may find that "in terms of psychological diathesis, older adults may be less vulnerable than younger adults."[3(p369)]

In an attempt to understand the various courses that aging may take, researchers have distinguished different types of aging. Primary aging (also known as normal, healthy, or usual aging) refers to changes in the aging process that are ultimately irreversible.[4] Core biologic features of aging such as a slowing of reaction time are considered part of primary aging. Secondary aging (or pathologic aging) refers to changes caused by illnesses that are correlated with age, but may be reversible or preventable. The division between normal and pathologic aging is based on the division between aging itself and age-related disease. This appears initially to be a purely biologic difference, but may in fact be determined by the current state of our medicine, which can reverse some age-related changes but not others. Would osteoarthritis shift from primary to secondary aging if a treatment were developed that reversed the joint disease?

Debates about what is normal aging and what is abnormal are relevant because morale in aging may be tied to what we think is normal versus abnormal aging. Morale may be more directly related to subjective age and health than objective age and health. Whether a person's health meets expectations may be more important than an objective description of a person's health state. These expectations are shaped by society, families, and personal history, as explained this way[5(p154)]:

> Aging is too often posed as a negative concept that implies loss and decline. Viewed from a life-course perspective, aging refers to the socially constructed and psychologically experienced passage of time.... It is precisely the social definition of the course of life that transforms the life span or life cycle into the study of the life course. There is explicit recognition that changes with age are a function of the shared definitions of expectable life events.

This social construction of aging may explain why most elders adapt to the losses of older years without the development of mental disorders.

Why is the preservation of morale important to primary care physicians? An aging population will carry an increased burden of chronic illnesses that cannot be cured, but must be managed. These illnesses bring with them aversive symptoms, disability, role dislocations, and challenges to well-being. This set of issues has been termed "health-related quality of life." The Institute of Medicine has given it top priority in the medical care of elders[6(p16)]:

> Health-related quality of life is perhaps the most important dimension of health outcomes for older individuals. Traditionally, the goal of health care has been to treat acute illness and delay or avert death. Increasingly, however, the goal of many older individuals and their families is not simply to add "years to life" but also to add "life to years."

Attention to morale may provide physicians with one of the most potent and cost-effective means of advancing health-related quality of life in their aging patients.

In the following sections, I will work backward from the most serious and rare outcomes of poor morale—suicide and major depression—to less serious but more common problems such as minor depression and grief, finally coming to a discussion of the emotional vulnerabilities and strengths of elders. Throughout, I will try to answer three questions:

- Why is aging not as emotionally threatening as might be expected?
- Why do some elders do better than others?
- How should medicine address these issues?

Suicide in Older Persons

Elderly persons commit suicide more often than any other age group. Younger women attempt suicide most often, but older men complete suicide most often. The suicide rate in the United States is 12 per 100,000. Among those older than 65, it is 20 per 100,000, a near doubling of risk. The highest rates are seen among older white men, where the rate is 43 per 100,000.[7] Depression and, to a lesser extent, medical illness have been identified as the primary risk factors for suicide in the elderly.[8] With aging, the association of suicide with depression and medical illness increases and the association with substance abuse and personality disorders decreases. There is a 30-fold increased risk of suicide in depressed patients than in the general population. The lifetime rate of suicide for depressed patients is as high as 19%.[9] The prototypical elder suicide is a chronically ill, socially isolated white man with a history of depression or substance abuse. The use of guns by this population means that many suicide attempts result in death.

What can physicians do? Pay special attention to those patients that have these risk factors. Actively assess these patients for suicidal ideation (this is never harmful), hopelessness (foreshortened future, "living from day to day"), and depressive symptoms. Refer suicidal patients for psychiatric treatment, even if they are chronically ill. As many as 75% of persons who commit suicide visit their primary care physician within the preceding month.

Major Depression

The Epidemiologic Catchment Area (ECA) study, a National Institute of Mental Health–directed study of mental disorders in the community, held some surprises for those interested in geriatric psychiatry. The prevalence of major depression among patients older than 65 was found to be 1.4% in women and 0.4% in men. This is a fourth of the rates found in the 18- to 44-year-old age group. This low rate of major depression has been explained as a product of a tendency of older persons to endorse somatic but not affective symptoms of depression, difficulty with the recall of symptoms, the increased stigma of depression among elderly persons leading to underreporting, and a cohort effect.[10] A cohort effect has been observed where persons born more recently show higher major depression rates, earlier age of onset, and higher relapse rates.[11] This could explain why older groups look less ill than younger ones in the absence of a true age effect.

The most likely explanation, however, is that there is a different pattern of depressive symptoms in the elderly. In addition to the low major depression rates among elderly persons, the ECA found that 2% of the community have dysthymia, 4% have adjustment disorder with depressed mood, and an additional 15% have subsyndromal depressive symptoms.[10] In the Established Populations for the Epidemiologic Study of the Elderly (EPESE) study, a curvilinear relation between age and depressive symptoms was noted, with the highest rates in young adults and those older than 75. Furthermore, it appears that this increase in depressive symptoms among the very old is not simply due to an increased endorsement of somatic symptoms. Controlling for illness, disability, income loss, and loss of relatives leaves a small negative relation between depression and age.[12] The picture that emerges from these studies is that the prevalence of dysphoria and other subclinical depressive symptoms increases with age, but these rarely reach the level of major depression. This means that depression is still a major problem in elderly persons. Of the 31 million Americans older than 65 years, 5 million have substantial depressive symptoms, with 1 million of these meeting the criteria for major depression.[13]

Risk factors for depression developing after age 65 include being female; being divorced, separated, or widowed; having low socioeconomic status; having poor social support, and having severe medical disability. Special risks have been noted with neurologic disease, endocrine disease, chronic obstructive pulmonary disease, myocardial infarction, and cancer. It appears to be important to distinguish groups with late and early onset among those with major depression. Many older adults with major depression have had previous episodes.[10] Those who have late onset without prior episodes have less family history of affective disorders, more neuropsychological impairment, and more areas of white matter hyperintensity on magnetic resonance imaging (MRI).[14] Late-onset major depression and minor depression may be mental disorders of late life, and early-onset major depression may be a recurrent lifelong mental disorder.

Medical comorbidity is the single most important factor that distinguishes older from younger depressed groups. It increases both the risk of illness and the risk of underdiagnosis. Depression is missed under the cover of chronic medical illness or explained away as a "reasonable" response to a bad situation. In structured interview studies, 7% to 36% of older medical outpatients have been reported to have major depression, at least a 5% increase over community rates; 40% of older medical inpatients have been found to have either major or minor depression; and 12% to 16% of nursing home residents have major depression, with other depressive disorders in 30% to 35% of institutionalized persons.[15] Although many elderly persons deny persistent dysphoria, questions about anhedonia can help sort out those with chronic illness who are depressed from those that are not. A personal interview using diagnostic criteria from the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders is always most sensitive,[16] but screening instruments such as the PRIME-MD[82] or the 15-item Geriatric Depression Scale[83] can be helpful.

Depression adds substantially to health care costs among elderly patients. In the Health Insurance Experiment of 4,829 fee-for-service patients, a poor mental health state was associated with greater inpatient but not outpatient costs after controlling for general health perceptions and physical health status.[17] This was considered relevant because inpatient costs accounted for 60% of total health care costs in this study. Researchers found that health care costs in all domains were markedly higher for health maintenance organization (HMO) members diagnosed with depression than for matched controls ($4,246 versus $2,371 per year). Only 20% of this difference was due to a difference in specialty mental health care. Especially important is the fact that costs were substantially greater for depressed patients at all levels of medical comorbidity.[18] In another study, similar results were found when looking at 5,012 HMO members older than 65. In a four-year prospective study, patients scoring over threshold on a depression scale had important increases in every component of health care costs, even after adjusting for the severity of chronic medical illness.[19]

The goals of depression treatment in elderly patients are multiple. It aims to reduce depressive symptoms, rates of relapse and recurrence, mortality, and health care costs. It aims to increase quality of life and physical and mental health status. An education program about depression was introduced for general practitioners in Gotland, Sweden, in 1983 to 1984. In the year following the program, there was less depression-related sick leave, 30% less inpatient care for depression, increased rates of antidepressant prescription, decreased rates of sedative-hypnotic and tranquilizer prescription, and decreased suicide rates. Within three years, all these measures had returned to baseline.[20]

Many elderly persons with depression who could benefit from treatment do not get it. The EPESE study showed that women were more likely to be treated with antidepressants than men and whites more likely than blacks. There was a suggestion that low socioeconomic status or very old age decreased the likelihood of treatment.[21] Obstacles to effective treatment include poor compliance, lack of family support, bereavement, social isolation, medical comorbidity, adverse side effects, hopelessness, and lack of integration of mental health with physical health services.[22] An effective negotiation strategy is essential for treating depression in the elderly. Agreeing with the patient that depression is due to overwhelming biologic or social stressors can help reduce its stigma. Coming to a jointly acceptable explanatory model for the depression will aid greatly in the patients' adhering to a treatment plan.

Depression treatments with proven effectiveness in the elderly include tricyclic antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, electroconvulsive therapy, cognitive-behavioral therapy, interpersonal psychotherapy, and possibly short-term psychodynamic therapy. Nortriptyline hydrochloride is the best-studied tricyclic antidepressant, with more than 300 patients treated in 20 clinical trials. Monoamine oxidase inhibitors are also well studied, especially phenelzine sulfate. It is important to remember that response may not occur for 6 to 12 weeks in elderly patients. Monitoring blood levels may be useful to verify compliance and to rule out toxicity. Relapse is best prevented with a continuation of full-dose treatment for at least 6 months after a first episode and 12 months after repeat episodes.[23] Selective serotonin reuptake inhibitors (fluoxetine, paroxetine, sertraline hydrochloride) have also been well studied and appear to be equal in efficacy to each other and to the tricyclic antidepressants, with the possible exception of the treatment of severe depression in the psychiatric inpatient setting.[24] Electroconvulsive therapy has high rates of response in severe depression (80% to 90%), but shows high rates of relapse (30% in 6 months), especially among those with a history of medication resistance.[25]

Among psychotherapies, cognitive-behavioral therapy, interpersonal psychotherapy, and possibly brief dynamic therapy have been proved effective.[26] The value of combined pharmacotherapy and psychotherapy is unclear. Remission appears more rapid with medication therapy. Remission rates are possibly higher when desipramine use is combined with interpersonal psychotherapy. Monthly interpersonal psychotherapy thereafter does appear to reduce recurrence rates.[27] Although there are developmental shifts in coping by elderly persons from problem-solving to reminiscence, problem-solving therapies have produced better results in controlled trials.[28]

There is increased risk for chronicity of depression among elderly patients. Studies of one to six years have shown chronicity rates of 7% to 30%. Rates can go as high as 40% if partial remission of major depression is included.[29] The risks for chronicity appear to be long current or previous depressive episodes, comorbid chronic medical illness, and severe depression, especially with delusions. Among those who do recover from major depression, there is a 13% to 19% rate of relapse or recurrence at one year. This is lower than the 34% rate of relapse-recurrence at the one-year point found in younger adults. But by three to six years, the recurrence rate in elderly patients is 38%.[30] Therefore, close follow-up of elderly patients in whom major depression develops is warranted.

Minor Depression

Depression that does not reach criteria for major depression is now being recognized as common and important, especially among elderly persons. Sometimes called "minor depression," this is most commonly defined as persistent dysphoria or anhedonia plus as many as three other depressive symptoms. Although major depression in elderly persons is often an exacerbation of a long-term mood disturbance, minor depression is often a response to the stresses of old age.[31] A prevalence of minor depression of 2.5% to 9.4% was found in one community study.[32] In another study, rates as high as 26.2% were found if dysphoria, dysthymia, and mixed anxiety-depression syndromes were included.[33] It was found that 47% to 52% of elderly medical outpatients met research diagnostic criteria for minor depression.[34] Nursing home studies have found rates of 18% to 30%. Studies of Department of Veterans Affairs populations have found prevalence rates of 18% to 29%.[35] The major risk factor for minor depression in elderly patients appears to be medical illness. The prognosis for the depression is worse if the illness is persistent and severe.

Much of the interest in minor depression stems from epidemiologic studies showing substantial disability and health care use to be associated with it. Investigators studied those in the community who had two to four depressive symptoms, including two weeks of dysphoria.[36] This minor depression group had a 53% greater chance of disability developing over the next year. Because of its higher prevalence, this group produced 51% more disability days than those with major depression. Over the next year, a major depression or anxiety disorder was also more likely to develop in this group.

There are as yet few treatment studies of minor depression. A multicenter study of minor depression in elderly persons is under way. In one study, patients with Hamilton Depression Scores of less than 13 showed no better response to the use of amitriptyline hydrochloride than to placebo, though those with scores of more than 13 did.[37] Response rates among those with Hamilton scores of less than 13 were as follows: 33% to placebo, 60% to imipramine hydrochloride, and 83% to phenelzine sulfate.[38] Patients with chronic minor depression or dysthymia show lower placebo response rates. Fluoxetine hydrochloride has been shown to be superior to placebo in the treatment of dysthymia.[39] A meta-analysis of psy-

chosocial treatments for depression in elderly persons showed efficacy for subsyndromal depression.[40] A recent study showed effectiveness for interpersonal counseling by a psychiatric clinical nurse specialist for the treatment of subsyndromal depression in medically ill elderly persons after hospital discharge.[41]

Grief

In the United States, 2 million die each year and an estimated 10 million are aggrieved. Our focus will be on the most serious grief: that associated with spousal bereavement. Each year 800,000 Americans lose their spouse. There are 11 million widows (mean age, 66) and 2 million widowers (mean age, 69) in the United States—7% of the population. The death of a spouse is associated with declining mental and physical health, suicide and nonsuicide death, and reduced income.[42] For an increasing number of elderly persons, the death of their spouse is preceded by years of intensive caretaking for Alzheimer's or other chronic diseases. Grief can thus begin before the actual death. The stages of grief do not follow any rigid sequence, but typically include a phase of denial, a phase of somatic emotional discomfort, and a phase of reorganization and recovery. Grief may last as long as two years. One study revealed that widows were often not recovered at 13 months after their spouse's death. Those who do recover "don't get over it, but get used to it."[43]

The following six dimensions of grief have been described[44(p530)]:

- Emotional and cognitive experiences—denial, autonomic explosion, yearning or pining, intrusive images of the deceased, anger, guilt, or regret, mental disorganization, and loneliness;
- Coping to regulate the amount of pain to what they can bear—numbness, intellectualization, distraction, and indulgence;
- A continuing relationship to deceased, realigning attachment bonds rather than giving them up—seeing deceased in heaven, seeing deceased in crowds, saving deceased's belongings, carrying out deceased's mission;
- Impaired functioning—substance abuse, mental disorders, decreased work and social performance;
- Reorganization of relationships—family, friends, new romance;
- Reshaping identity, from helpless and overwhelmed to new strength and autonomy.

These are not experienced in any set order. They can all be part of normal or uncomplicated grief.

Grief can become complicated. The risk factors for complicated grief include characteristics of the death (multiple, sudden, stigmatized, or child deaths), characteristics of the relationship to the deceased (an ambivalent or dependent relationship), and characteristics of the bereaved (poor health, poor support, or severe concurrent stresses). Three types of complicated grief have been described.[44] The first is absent or inhibited grief and is seen when there was a deeply ambivalent or dependent relationship to the deceased or no deep attachment. The second is hypertrophic grief, which is characterized by especially severe symptoms, although it usually attenuates over three to four months. Early intense symptoms are associated with subsequent depression, however. The third is chronic grief, which is characterized by unrelenting sorrow and idealization of the deceased. It produces a pervasive preoccupation that lasts longer than a year. It is most commonly seen in child and unnatural (suicide, homicide, accidental) deaths.

Grief has various adverse consequences that are more pronounced when grief is complicated. Mortality is increased in widows and widowers, especially among young widows and the oldest old. Aggrieved persons have more somatic symptoms, more medical visits, more accidents, and higher rates of suicide. Substance abuse, anxiety disorders, and post-traumatic stress disorder are common in the first year.[45] Intermittent depression is common[46]; 29% to 58% meet major depression criteria at one month, 24% to 30% at two months, and 25% at three months. Depression associated with grief typically has less associated guilt and worthlessness, but may have similar sleep disturbance.[47]

Some treatments have been shown to reduce the suffering associated with grief. Prebereavement counseling can be helpful, especially as a part of hospice care. Mutual support groups for aggrieved persons appear to be as effective as brief dynamic therapy.[48] Antidepressants appear to help those with persistent depressive symptoms, even if they do not reach major depression severity.[49]

Sources of Vulnerability to Affective Decline in Elderly Persons

Biologic

Some of the neuroendocrine alterations found in persons with major depression show age effects and may provide a source of vulnerability to depression for the aged. Low urine and plasma methoxyhydroxyphenylglycol levels, as well as increased α_2-adrenoreceptor binding (suggesting decreased noradrenergic function), appear more typical of early-onset than late-onset depression.[50] High platelet monoamine oxidase activity, a possible marker for bipolar disorder, also appears to be present in late-onset depression, especially in patients with early dementia.[51] Low platelet imipramine binding, a measure of serotonergic activity, has been noted in geriatric patients with depression.[52] No consistent pattern of neuroendocrine vulnerability has emerged as yet.

Neurologic disease holds clear risks for depression in the elderly. Among those who become demented, depression will develop in about 50%. In patients with

Alzheimer's disease, depression rates of 17% to 31% are most reliable.[53] In those with stroke, 24% have been found to have depression. The risk appears to be highest among those with left frontal infarcts and premorbid cortical atrophy.[54] A 50% rate of depression has been found in patients with Parkinson's disease. This does not appear to be related to the degree of motor impairment.[55] A variety of changes on MRI have been associated with depression: enlarged lateral ventricles, cortical atrophy, more frequent periventricular hyperintensities (primarily enlargement of perivascular spaces), more frequent deep-white matter lesions (associated with depression but also risk factors for cardiovascular accidents), more frequent basal ganglia lesions, and smaller caudate and putamen.[56] The import of these MRI findings is not yet clear.

Chronic medical conditions predispose elderly persons to depression through two possible mechanisms: an increased burden of aversive symptoms and increased disability. Pain is reported by 78% of young old (aged 60 to 69) but only 64% of old old (aged 80 to 89) independent healthy persons. In institutional settings, 71% to 83% of patients report at least one pain symptom.[57] Some investigators have asked whether the relation between pain and negative affect changes with age. Two of three studies have found that elderly patients with chronic pain report less anxiety than younger patients.[58] Another study found that depression and pain intensity levels were more strongly correlated in older than younger patients. This was true despite the fact that the older patients reported lower levels of pain intensity and interference.[59]

Several large studies have documented that poor perceived health and a number of preexisting conditions predict functional decline. New events such as myocardial infarction, cardiovascular accident, cancer, or hip fracture predict more decline than a condition present at baseline.[60] Vision and hearing impairments also predict functional decline, as do nonmedical factors such as socioeconomic status. Cognitive impairment impedes a person's adaptation to disability.

The critical factor linking disability and emotions may be the sense of personal control.[61] Supporting this theory is the finding that physical self-efficacy is a better predictor of depressive symptoms than objective health status.[62] Adding interest to this finding is the discovery that older persons show less erosion of self-efficacy with disability than younger patients. It has been hypothesized that illness was seen as a greater "relative deprivation" in the younger patients.[63] These clinical findings are consistent with population-wide findings showing changes in historical standards of good health. Later birth cohorts have better physical health and less disability than earlier cohorts, but a smaller proportion report good health.[64] In general, subjective reports of health are not as strongly related to age as are objective measures.[65] Self-rated health is more strongly associated with the recovery of physical function after a medical event than are objective measures of health.[66] In fact, self-rated health—after controlling for objective measures—predicts survival 4 years, 9 years and 12 years later.[67]

Psychological

It appears that disability erodes affect when it decreases self-efficacy or the confidence to perform specific behaviors. Four sources of self-efficacy have been discussed: past and present experience of performance, observing others perform, social influence, and states of physiologic arousal. Experiences with symptoms and disability and social expectations will shape a person's confidence.

Personality does not appear to be a factor that increases vulnerability with aging. Some personality disorders may get better with age (borderline, antisocial, narcissistic), and some may get worse (paranoid, compulsive, schizotypal). In general, self-concept and self-esteem appear to be relatively stable with aging. This may reflect a growing coherence of the life story with aging. By late life, the life history report is an important indicator of well-being, especially for elderly persons in institutions.[68]

Social

Disrupted personal relationships constitute the primary social source of vulnerability to affective decline in older age. Social isolation is itself a risk factor for poor mental and physical health,[69] but the loss of previously established relationships through death or divorce appears more potent than their simple absence. Widowhood, for example, produces 48% excess mortality in men at 3 months, and the effect is apparent for as long as 11 years later.[70] A critical factor, once again, in determining the effect of these losses is whether they are expected or not. "On-time" role transitions pose less of a threat to morale than "off-time" events such as early widowhood.

Protective Factors

Social

Although generally a positive relation exists between social support and morale in old age, a decline in the size of the social network may not signify a deterioration in social support for the elderly. Elderly persons may have fewer social relations, but may have selected those where they can be understood, share intimately, and express difficult emotions.[71] Neglected aspects of the social network for elderly persons that may be especially important are avenues for giving and receiving social support. In a study of community-dwelling elderly persons, helping others was the most potent predictor of social integration and self-esteem.[72]

Religion plays an important part in the life of many older persons: 52% attend weekly religious services, 25% pray three times a day, 27% read the Bible two to three times per week, and 64% watch religious television shows.[73] Sociologists view religion as serving two main functions: providing meaning in the face of the unknown and stabilizing the social group. Those who view religion from the inside define it as "a search for significance in ways related to the sacred."

More than 200 studies have demonstrated a positive relationship between religion and health indicators.[74] Religion may allow older persons to experience life as meaningful despite losses and challenges. Some plausible hypotheses about the sources of religious feeling have not been validated by research. For example, religiosity does not appear to be associated with personality,[75] it does not appear to increase substantially with age, and its effect on life satisfaction does not increase substantially with age.[76]

Psychological

In general, there is a lowered intensity of emotion and affect in elderly persons. The elderly appear to conserve their emotions better. "They are seen to afford fewer and fewer persons the power to affect them profoundly."[71 (p223)] Older people are more selective in their "comparison targets" by which they gauge their self-esteem. In fact, they appear to do less social comparison with others and more temporal comparison with their earlier selves.

Older adults report a more limited range of self-categories (hoped-for versus feared possible selves). Their self-images were tied more closely to ongoing experience. This stands in contrast to younger adults who were more idealistic and future oriented. "The result was less conflict between unrealized goals for older adults."[77(p241)] "[W]ith the advent of late life, the number of possible role transitions diminishes.... in general, there are fewer unexpected life events serving as sources of distress among older adults.... the expectable nature of the losses has different significance for adjustment."[5(p157)] Fundamental to this change in expectations is a recognition of the finitude of life. The recognition that "there is less time to be lived than has been lived already" begins in the fifth decade of life. As it occurs, this recognition can prompt a mid-life crisis. Those who accomplish it begin to look backward for inspiration and meaning rather than looking to finding a time of realization in the future. There is generally more introspection and more preoccupation with the meaning of life, including personal accomplishments and disappointments. Men appear to become less focused on mastery and more on comfort, but women shift toward instrumental mastery and away from an identity based in relationships.[78]

This shift in attitude manifests itself in a shift from assimilative or instrumental coping styles to accommodative coping styles that use disengagement. A number of investigators have claimed that morale in old age can be understood adequately only if developmental transitions in the employment of control strategies are considered. Older adults are prone to use emotion-focused rather than problem-focused coping. This is usually less adaptive in younger years but may be appropriate in later years. Middle-aged adults reminisce to cope; older adults reminisce to reconcile.

This difference in coping styles is critical to understanding the differential effects of health events in younger and older adults. Although the most "feared selves" that older adults face concern health, they appear less distressed by health crises and better able to confront death than younger adults. But the health problems that affect morale most adversely are those that cannot be coherently incorporated into a life story. Arthritis and diabetes mellitus appear to be handled better than vertigo, bladder trouble, and difficulty walking, where cause and treatment are less clear-cut.[79] Older adults generally think of themselves as healthy[80(p.351)]:

> Despite health worries and ailments, older adults tend to describe their health as good. Indeed, among those ages 65 or older, there does not appear to be an increase with age in the proportion of individuals who regard their health as poor, even though the incidence of health problems does increase.

Elders compare themselves with their peers and with their expectations of old age. Their satisfaction is not closely tied to where they stand on objective indices of health. This said, maintaining independent functioning appears particularly important in our culture. Continued physical mobility appears essential to well-being.

There are distinct decreases in the intensity of affect with age. The Berlin Aging study found that the frequency of positive affect decreased slightly in older age groups, but that negative affect did not increase.[81] Although Eric Erikson talked about the attainment of wisdom as the developmental challenge of old age, few seem to accomplish this. It appears more common for elders to develop a sense of acceptance rather than a new broader perspective. Young and middle-aged adults associate being wise with being older, but older adults do not. Equanimity would seem a better name than wisdom for the affective state commonly achieved by elders.

Conclusion

> *What, in ill thoughts again? Men must endure*
> *Their going hence, even as their coming hither:*
> *Ripeness is all.*
>
> WILLIAM SHAKESPEARE
> *King Lear*

Aging does not produce despair for most people because they expect a diminishment of life's energy and capacities. This is experienced by most not as a horrible deprivation, but as a rounding off of life's possibilities. Subjective health is more important than objective health for morale—and probably quality of life—in our later years.

Some elders do not recover from grief, do become depressed, and may commit suicide. Those most at risk often have a history of mental disorders and substance abuse before their old age. Chronic illness and disability appear to play a major role in the minor depression that is typical of old age. Better efforts by medicine at symptom and disability reduction will help prevent these depressions. Better recognition of depressive symptoms in the presence of medical illness will help elders receive beneficial treatment. The preservation of good morale

has an important part to play in maximizing the quality of life of our aging population. It may be an important part of what makes another year of life worth living.

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SUCCESSFUL AGING

Aging and Sexuality

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Recent research suggesting that a high proportion of men and women remain sexually active well into later life refutes the prevailing myth that aging and sexual dysfunction are inexorably linked. Age-related physiological changes do not render a meaningful sexual relationship impossible or even necessarily difficult. In men, greater physical stimulation is required to attain and maintain erections, and orgasms are less intense. In women, menopause terminates fertility and produces changes stemming from estrogen deficiency. The extent to which aging affects sexual function depends largely on psychological, pharmacological, and illness-related factors. In this article I review the physiological sex-related changes that occur as part of the normal aging process in men and women. I also summarize the effects on sexual function of age-related psychological issues, illness factors, and medication use. An understanding of the sexual changes that accompany normal aging may help physicians give patients realistic and encouraging advice on sexuality. Although it is important that older men and women not fall into the psychosocial trap of expecting (or worse, trying to force) the kind and degree of sexual response characteristic of their youth, it is equally as important that they not fall prey to the negative folklore according to which decreased physical intimacy is an inevitable consequence of the passage of time.

(Meston CM. Aging and sexuality. In: Successful Aging. West J Med 1997; 167:285–290)

[My] ... Age is as a lusty winter,
Frosty, but Kindly.

WILLIAM SHAKESPEARE
As You Like It[1]

Sexual desire and activity continue well into later life for both men and women but can be affected in various ways by aging. I begin by discussing these effects in men.

Men

Although an age-related decline in sexual activity and desire among men has been reported in numerous studies, maintaining a healthy interest in sexual activity is not uncommon among 70-, 80-, and even 90-year-old men. Pfeiffer and associates[2] reported that 95% of men aged 46 to 50 years and 28% of men aged 66 to 71 years have intercourse on a weekly basis. Diokno and co-workers[3] have reported that nearly 74% of married men older than 60 remain sexually active, and Bretschneider and McCoy[4] found that 63% of men aged 80 to 102 years continue to be sexually active. In view of the fact that sexuality in the literature is often defined exclusively in terms of intercourse, these estimates would probably be even higher if noncoital acts such as touching, caressing, fantasy, and masturbation were taken into account.

The age-related decrease in libido noted among men is most frequently attributed to a decline in testosterone levels and to changes in receptor site sensitivity to androgen. The sex hormone status of a healthy man remains relatively stable from puberty until the fifth decade of life, at which time androgen production gradually declines. The first sign of an alteration in endocrine function is a small increase in pituitary-stimulating hormone levels (gonadotropins), which signals the relative inability of the aging testes to efficiently produce testosterone.[5] Serum testosterone levels gradually decline as a consequence, and by age 80 they may be only a sixth those of a younger man.[6] Although the drop

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in serum testosterone levels clearly parallels the decline in sexual libido noted with age, there is little evidence to suggest that testosterone replacement therapy augments sexual drive in men with normal baseline testosterone levels. That is, administering massive doses of androgen to an 80-year-old will not restore his libido to what it was when he was 18.[5]

There appears to be a minimal level of testosterone necessary for adequate sexual functioning, above and beyond which additional amounts have no effect. This probably reflects limitations set by the number and sensitivity of functional testosterone receptors. Because most older men apparently have these receptors in numbers above the "critical" level, it is generally assumed that exogenous testosterone would be superfluous and would not restore age-related decreases in sexual drive. Using a placebo-controlled design, Morales and associates[7] examined the effects of exogenously administered adrenal androgen dehydroepiandrosterone (DHEA) on a number of age-related factors in 13 men aged 40 to 70 years. When levels were restored to those of a younger age group, DHEA had no direct effect on sexual interest. Replacement DHEA did, however, have a beneficial effect on general measures of well-being. Such measures may, in turn, have a positive effect on sexual satisfaction and function. Further studies of the effects of DHEA on male sexual function and well-being are required before treatment considerations are warranted.

Women

A decline in sexual interest and desire is frequently reported to be more severe in aging women than aging men. Such assertions are often based on studies that compare the incidence of sexual activity in aging men with that in aging women. For example, recent research indicates that approximately 56% of married women older than 60 (compared with 75% of married men) are sexually active,[3] as are approximately 30% of women aged 80 to 102 years (compared with 63% of men).[4] As noted earlier, sexual interest and activity in studies of this nature are too often measured solely according to frequency of intercourse. Given that by the age of 80 or older there are 39 men for every 100 women,[8] lack of opportunity may well account for a large portion of such gender differences. More importantly, gender differences in the incidence of intercourse and masturbation are apparent in adolescence and throughout adulthood,[9] not only among older people. Hence, age-related changes in sexual activity may best be understood by examining change across a person's total lifespan rather than comparing incidence between genders. To this end, the Janus report[10] indicated surprisingly little change in sexual activity across the average woman's lifespan. In this report, 68% of women aged 39 to 50 engaged in sexual activity at least once a week, as did 65% of women aged 51 to 64 and 74% of women older than 65. As is the case in men, masturbation frequency in women has been noted to decline with age, but it continues to be practiced by approximately half of the healthy female population over the age of 60.[12] In contrast to research indicating that sexual desire declines with age, 9% of women interviewed for a Danish study[13] reported an increase in sexual desire during or after menopause.

One of the primary causes of decreased sexual desire in postmenopausal women is decreased vaginal lubrication or a thinning of the vaginal lining, both of which may lead to pain during vaginal intercourse. In such cases, sexual desire generally returns once some form of treatment (for example, estrogen or lubricants) has relieved the symptoms.[14] A lack of bioavailable testosterone may also reduce sexual desire in women. Although there is no absolute level of testosterone necessary for sexual desire, it has been suggested that there is a threshold level of circulating androgen below which the intensity of desire is affected.[15] It is not clear why some menopausal women experience a sharp decline in testosterone production,[14] nor has it been proved that androgen replacement therapy is of more than marginal therapeutic value in such cases.[15] More importantly, the safety of prescribing testosterone is currently controversial. Testosterone may affect cholesterol and liver protein levels; at high doses, it may also cause masculinizing effects such as facial hair or lowered vocal pitch.[14] Researchers have recently examined the effect of the adrenal androgen DHEA on the sexuality of women aged 40 to 70 years.[7,16] Although neither circulating nor replacement levels of DHEA were directly linked to measures of sexuality in women, DHEA was significantly associated with measures of overall well-being.[7,16] Well-being in turn was shown to be predictive of the quality of sexual relationships.[16] Further studies of this nature are required before suggestions for treatment can be made.

The less frequent reports of increased sexual desire among older women may also be explained by hormonal changes that occur following menopause. When estrogen levels decline, levels of follicle-stimulating hormone and luteinizing hormone increase in an effort to stimulate estrogen production. The increase in these two hormones stimulates certain cells in the ovarian stromal tissue to produce testosterone. Women vary widely with regard to efficiency in producing testosterone in this manner.[14] Women who have an increase in testosterone production during or after menopause may possibly have increased sexual desire. Psychological factors such as elimination of the fear of conception may also play a role in increasing sexual desire after menopause.[14]

Physiologic Aspects of Aging and Sexuality in Men

With regard to actual physiologic changes that occur with age and affect sexual functioning, much individual variation exists. It has been estimated that 55% of men experience impotence by the age of 75.[17] This should not be taken to mean that erectile failure is a normal stage in the aging process. The alterations that lead to decreased sexual functioning, particularly erectile failure, are

multifactorial, made up of elements that may be both organic (such as the effects of disease or medication) and psychological (for example, anxiety and guilt). It is clear that all stages of the human sexual response cycle, as defined by Masters and Johnson,[18] are influenced by age-related factors, but there is no evidence to suggest that erectile failure is inevitable among aging men who are psychologically and physiologically healthy.

The Sexual Response Cycle

Normal age-related changes that accompany the excitement stage of sexual response in men include a decrease in, or lack of, elevation in testosterone levels; a decrease in scrotal vasocongestion; reduced tensing of the scrotal sac; and delayed erection. Where a young man may achieve a full erection in seconds, an older man may require several minutes to attain a similar response. Age-related changes in adrenergic and cholinergic mechanisms may partly explain these changes. The process of erection is a vascular event mediated by the autonomic nervous system. Corporeal smooth-muscle tone plays a primary role in erectile ability; gap junctions and ion channel mechanisms, in turn, are largely responsible for determining the degree of smooth-muscle tone.[19] With advancing age, there is evidence that a decline occurs in the number of β-adrenergic and cholinergic receptors, which may lead to increased dominance of α^1-adrenergic activity (that is, increased corporeal smooth-muscle tone). This in turn may interfere with the corporeal smooth-muscle relaxation necessary for initiation and maintenance of the erectile response.[19] Age-related cellular changes may also negatively affect the erectile response through an increased deposition of connective tissue, causing a decrease in penile distensibility.[19] This loss of corporeal elasticity may lead to lowered compression among emissary veins, resulting in venous leakage and consequent difficulty achieving erection.

Penile sensitivity also decreases with age.[20] Attaining and maintaining an erection, therefore, becomes more dependent on direct physical stimulation and less dependent on, or responsive to, centrally controlled visual, psychological, or nongenital excitation.[19] As a result, partners may need to facilitate the erectile response by providing manual or oral stimulation before intromission and possibly at periods throughout the sexual act to help sustain erection until orgasm. Penile rigidity declines gradually, beginning in most men at age 60.[19] Generally, rigidity remains adequate for vaginal intercourse, but couples may need to experiment with different coital positions or supplement intercourse with manual stimulation.

The plateau stage of sexual response is prolonged with age, and pre-ejaculatory secretions and emissions are reduced or cease to occur. Prior difficulties with premature ejaculation may be resolved in older men because of the increase in stimulation and time required to reach orgasm. The duration of orgasm decreases with age, there are fewer and less intense spastic prostate and urethral muscle contractions, and there is a decrease in expulsive ejaculatory force. The period of inevitability before ejaculation is reduced from between 2 to 4 seconds in younger men to approximately 1 second in older men, and there is a slow but gradual decline in semen volume per ejaculation.[19] Occasionally orgasm may occur without ejaculation. The final postorgasmic or resolution stage of sexual response is marked by more rapid loss of vasocongestion and an increase in the length of the refractory period. For a man in his 20s the refractory period may last only minutes; for a man in his 80s it may extend to several days—probably the amount of time required for ionic and neurotransmitter concentrations to be restored to normal levels.[19]

Physiologic Aspects of Aging and Sexuality in Women

Effects of Menopause

Menopause, which occurs in most women at about age 50, is associated with substantial reductions in estrogen, progesterone, and androgen levels. Following menopause, estrogen is almost exclusively derived from the peripheral conversion of adrenal androgens. Around age 65, there is a further decrease in adrenal androgen production, often referred to as adrenopause.[15] The decline in estrogen that accompanies menopause leads to a number of normal age-related changes in genital appearance. Such changes include a reduction in pubic hair, loss of fat and subcutaneous tissue from the mons pubis, atrophy of the labia majora, and shortening and loss of elasticity of the vaginal barrel. Vaginal secretions decrease in quantity as a result of both atrophy of the Bartholin glands and a decrease in the number and maturity of vaginal cells. The vaginal epithelium, which is highly estrogen dependent, becomes flattened and loses glycogen; this leads to a decrease in *Lactobacillus* species and lactic acid and an increase in vaginal pH.[21] These alterations affect the vaginal microbial population and put aging women at greater risk for developing bacterial infections.[22] Together with decreased vaginal lubrication, the reduction in thickness of the epithelium from approximately eight to ten cell layers to three to four may lead to postcoital bleeding, mild burning sensations during intercourse, and pain.[22] For such reasons, dyspareunia is the most common sexual complaint among older women seeking gynecologic consultation.[23] With decreased estrogenic stimulation, the uterus is reduced in size and the total collagen and elastic content decreases by 30% to 50%.[24] The uterine cervix also atrophies and loses fibromuscular stroma, and the ovaries, with no remaining follicles, become reduced in size and weight and the ovarian stromal tissue becomes fibrotic and sclerotic.[22] Estrogen replacement therapy, when given systemically at high doses, has a beneficial effect on urogenital tissue[22] but is associated with an increased risk of breast and endometrial cancer.[25] In the absence of other postmenopausal symptoms, vaginal estrogen cream administered a few times per week may be equally effective.

The Sexual Response Cycle

A number of age-related changes affect the female sexual response cycle. During the excitement phase, vaginal blood flow and genital engorgement are less intense than in younger women and take longer to occur. This phenomenon may be less pronounced in women who continue to be sexually active than in those who are celibate, although its mechanism is not well understood.[15] Vaginal lubrication is delayed and reduced in quantity. Whereas in younger women the excitement stage with lubrication may take only 10 to 15 seconds, in postmenopausal women it may take as long as 5 minutes or longer.[26] The decrease in vaginal vasocongestion and lubrication may contribute to dryness of the vagina and may make intercourse painful. A variety of topical lubricants have been used successfully to compensate for insufficient vaginal lubrication. For women who prefer not to use a lubricant during intercourse, nonhormonal preparations such as Replens or oil from a vitamin E capsule, applied vaginally every other day, may greatly alleviate vaginal dryness, as may taking zinc orally.[14] Despite these age-related physiologic changes, several studies have reported that postmenopausal women report little or no change in the subjective experience of sexual arousal.[27]

The plateau phase of sexual response is prolonged in older women, uterine elevation is reduced, the labia majora do not elevate to the same degree as in younger years, the breasts become less vasocongested, and nipple erection is less likely to occur.[1,15] The orgasmic response does not appear to be substantially affected by age. Women retain multiorgasmic capacity, although the number and intensity of vaginal and rectal contractions are reduced.[5] While younger women average five to ten vaginal contractions with orgasm, older women average two or three.[5] As is the case in men, the resolution stage of sexual response in older women is characterized by a rapid loss of vasocongestion.

Illness, Medication Use, and Sexuality Among Older Persons

Physical illness can affect sexual function directly by interfering with endocrine, neural, and vascular processes that mediate the sexual response, indirectly by causing weakness or pain and psychologically by provoking changes in body image and self-esteem. The scope of this article precludes a comprehensive discussion of the effects of medical illness on sexuality; accordingly, only the most prevalent age-related medical illnesses, prescribed medications, and their effects on sexuality will be mentioned here (for a review, see Badeau[28]).

Men

Medical or surgical therapy for a number of age-related diseases can affect erectile function by interfering with the neurologic innervation of the penis. Interventions that may have this effect include lower abdominal surgery, pelvic irradiation, and certain types of prostate surgery.[5] Transurethral resection of the prostate has been reported to cause erectile failure in 4% to 12% of cases.[2] Radical prostatectomy for prostate cancer, cystectomy for bladder cancer, and colorectal surgery may all damage the neuromuscular bundle of the penis. Although increasing attention has been paid to preservation of the neurovascular bundle, men with aberrant cavernous arteries more often than not suffer erectile dysfunction from such procedures.[19] A number of age-related disease states may interfere with erectile function directly. The atherosclerosis associated with cardiovascular disease may involve the penile arteries as well as the coronary arteries. Occlusion of the abdominal aorta or the iliac arteries may also be associated with the failure to attain erection.[5] Because the act of intercourse increases heart rate and blood pressure, fear of chest pain during intercourse may further impede sexual relations. Diabetes mellitus is commonly associated with erectile failure. Within only five years after the onset of type II disease, 60% of male patients have some form of sexual dysfunction.[19] The causes of erectile failure in diabetic men are largely neurogenic and vascular, but also include alterations in corporeal smooth-muscle reactivity and microangiopathy, which may cause arterial insufficiency.[19] Somatic and autonomic neuropathy may produce neurogenic impotence in older diabetic men. Other endocrine or metabolic disorders associated with erectile problems include hypothyroidism, hyperthyroidism, hypogonadism, hyperprolactinemia, and Cushing's disease. Systemic disorders known to impair erection include renal failure, chronic obstructive pulmonary disease, cirrhosis, and myotonia dystrophica. Among the neurologic disorders that may inhibit erection are spinal cord injury, cerebrovascular accidents, temporal lobe epilepsy, multiple sclerosis, and sensory neuropathy.[1,5]

A wide variety of drugs have been reported to impair erectile ability, particularly among older persons. The aging process influences physiologic drug distribution, metabolism, and excretion and renders older persons more vulnerable to the side effects of medication.[19] Among medications, antihypertensive agents that act either centrally (for example, methyldopa and clonidine) or peripherally (for example, reserpine, guanethidine), β-blockers (such as propranolol or labetalol), α-blockers (including prazocin and terazocin), and diuretics (for example, thiazide and spironolactone) appear to be the primary offenders in causing impaired erection.[19] In addition, cardiovascular drugs (such as disopyramide), cancer chemotherapy agents, anxiolytics (benzodiazepines), antipsychotics (for example, haloperidol, thioridazine, and chlorpromazine), a wide range of antidepressants (such as imipramine, amitriptyline, trazodone, and fluoxetine), lithium, and numerous drugs of abuse (including cocaine, alcohol, narcotics, and amphetamines) have all been linked to impaired erectile function (for reviews, see Schiavi and Rehman[19] and Meston and Gorzalka[30]). With diseases such as depression, hypertension, and atherosclerosis, it is difficult to determine the extent to which the sexual dysfunction is a result of the

prescribed medication or the disease per se, given that both may negatively affect the sexual response.

Women

Surgical treatment of gynecologic and breast cancer often has a deleterious effect on sexual function in women by assaulting body image. Although breast or vulvovaginal surgery undoubtedly affects self-esteem in women of all ages, the psychological damage may be further compounded in older women whose body image is perhaps already affected by age-related body changes. Urinary incontinence occurs in up to 25% of older women during intercourse.[31] This disorder commonly leads to dissatisfaction with the sexual relationship or withdrawal from sexual contact because of embarrassment. Renal failure has been reported to cause anorgasmia, decreased libido, and impaired vaginal lubrication in women on dialysis.[1]

Hysterectomy is the most commonly performed operation in women: more than a third of women in the United States have had a hysterectomy by age 60. This procedure has not been shown to have a direct effect on sexual function; some women, however, report a decline in orgasmic pleasure following hysterectomy because of the absence of uterine contractions. For women who view hysterectomy as a further loss of femininity, self-esteem and body image may be damaged by this type of surgery. Conversely, for women who experience relief from pain, abnormal bleeding, or cramping, hysterectomy may result in improved sexual function.[1]

In contrast to an abundance of research on diabetes and male sexual function, there is a paucity of studies examining the effects of diabetes on female sexual function. Decreased sexual desire, anorgasmia, and difficulty obtaining sufficient vaginal lubrication during sexual arousal have been identified in some women with type II diabetes mellitus.[5,15] The duration of diabetes, age, or insulin dosage does not appear to be correlated with sexual function among women with diabetes,[32] and there is no evidence that peripheral or autonomic neuropathies directly affect the female sexual response.[15]

Research into the effects of medication use on sexual function in women has lagged considerably behind that in men. Antidepressant drugs are commonly reported to affect sexual functioning in women. Side effects associated with antidepressant medications include decreased sexual desire, impaired arousal and lubrication, vaginal anesthesia, delayed orgasm, and anorgasmia (for a review, see Meston and Gorzalka[30]). Serotonergic systems are frequently implicated in antidepressant-induced sexual side effects, although data are inconsistent as to whether the role of serotonin in sexual behavior is inhibitory, excitatory, or both.[30] Antipsychotic and neuroleptic medications have also been linked to impaired sexual function in women. Most recently, the antihypertensive drug clonidine has been shown to impair physiologic sexual response in women by decreasing vaginal blood volume and pressure pulse responses.[33] Clearly, there is a need for further research in this area.

Psychological Aspects of Aging and Sexuality

Not surprisingly, a number of psychological factors that influence the sexuality of younger persons also affect older men and women. Of particular importance is the nature of the interpersonal relationship. Marital conflict, relationship imbalances, commitment issues, intimacy and communication problems, lack of trust, mismatches in sexual desire, boredom, and poor sexual technique are just some of the common sources of sexual dissatisfaction noted among couples of all ages.[5,34] In older people these factors may be amplified by anger and resentment that may have built over the years, as well as by feelings of entrapment and resignation if the option to leave the relationship no longer seems viable. As with younger couples, marital satisfaction is closely linked to sexual satisfaction in older couples.[34]

Increases in psychosocial stresses, such as the death of a spouse, loss of a job or social status, deterioration of support networks, and health- and finance-related family problems, are common experiences among the aged. These life changes may contribute to sexual difficulties in older people by increasing the likelihood of depression or anxiety. "Widower's syndrome" refers to the onset of sexual difficulties in older persons who resume sexual interactions after a period of celibacy following the death of a spouse. Sexual difficulties in this situation are generally attributable to unresolved feelings of grief, guilt, anger, or even relief in cases in which the partner had been ill for a long period before death.[5] Performance anxiety related to beginning a new sexual relationship may be a problem for both men and women, but may play a particularly detrimental role in male sexual function because of the well-known adverse effects of anxiety on erectile function.

Because women generally marry men older than themselves, and are likely to outlive men by an average of seven to eight years, women are more likely than men to experience the death of a spouse in old age. Given the shortage of available older male partners, women are also more likely than men to spend the later years of life alone. Many older women report feeling sexually frustrated at the lack of an available sexual partner. Although masturbation is a viable option, older persons may have been brought up to believe that masturbation is unnatural or even unhealthy. Education and permission from a health care professional may help to alter such misconceptions.[5] Also common among older people are false expectations regarding the effects of aging on sexuality. Self-critical anxieties about one's sexual abilities or physical imperfections can be distracting or even destructive to sexual pleasure and excitement. The societal emphasis that has linked sexuality almost exclusively to young people may lead some older people to feel ashamed of their continued sexual interest and may consequently discourage them from seeking sexual advice. Information from physicians regarding normal age-related changes in sexuality and encouragement, together with advice on how to continue meaningful sexual relations, may play a key role in altering such negative attitudes.

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SUCCESSFUL AGING

Community Resources for Frail Older Patients

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The goal of community-based services for frail older patients is to help them achieve the greatest degree of functional ability and independence. The services available include case management, geriatric assessment, adult day health care, home health services, and the Program for All-inclusive Care for the Elderly (PACE). Definitive criteria for referral have not been established, but without some targeting, the efficacy of these services remains uncertain. Targeting criteria identified include dependency in 2 or more activities of daily living, no family support, dementia, many long-term illnesses, and many hospital stays. Although efficacy and cost-effectiveness remain uncertain, patients, families, and physicians generally report these services to be helpful.

(Borgenicht K, Carty E, Feigenbaum LZ. Community resources for frail older patients. In: Successful Aging. West J Med 1997; 167:291–294)

Older patients are much more likely than young to require community resources when they are ill. Young and middle-aged adults usually seek medical attention for an acute illness that, in most instances, resolves quickly, and the patients resume their normal lives. Geriatric patients have chronic illnesses, multiple medical problems, slow recovery often with decreased mobility and function, and associated social and psychological problems, especially if they live alone or with a sick spouse. Thus, social services and other community resources are often needed. In the past 30 years, older patients faced with progressive weakness and disability had few options available to help them remain at home. In addition, because nursing home placement was reimbursable (but in-home personal care services were not), physicians and families often took the more economical route and placed patients in nursing homes when other alternatives might have served them better. We will briefly discuss some of the community resources now available to frail older patients that often will allow them to remain at home or at least delay admittance to a hospital or nursing home.

We will also describe those patients appropriate for different services and how these services can help maintain the greatest degree of independence possible for the patients. It should be noted that the theme for this edition is successful aging. Why, then, an article on frail older patients? The answer is that geriatric medicine looks for those strengths and resources within patients, families, and the community that can increase the patients' potential for success. Stroke patients who progress from bedbound to chair and finally to walking should be recognized as a variant of successful aging.

Community Services Available

Case Management

The primary goal of case management is to identify and to coordinate the community services persons may need to live at home in the least restrictive environment possible. Case-management programs typically include the following services: evaluation and supervision of patients' health, functionality, and psychosocial status; advocacy; referral to services; coordination of services; and consultation with physicians. Services can be difficult to access, and the needs of older people can change as their conditions change. Case managers, who are usually nurses or social workers, not only navigate their way through the fragmented service community, but they can also tailor services to the individual needs of their clients.[1]

The term "case management" is now being used in a wide variety of settings, and the goals may differ in

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each setting. For example, a case manager at a nursing home or hospital will focus on the short-term goals of discharge planning and the arrangement of home care services immediately following the nursing home or hospital stay. They do not usually have responsibility for follow-up care or discharge. The responsibilities of case managers working for managed care groups may have the additional responsibility of managing the resources within the health care program with the goal of minimizing expenditures for services. A community-based case manager, common in many local and state-funded programs, will not only arrange services for a patient but will actively monitor those services and the patient's needs.

Case management can be an invaluable adjunct for physicians by helping to manage complicated older patients in the community. A number of case-management programs provided by Medicare managed care organizations assign case managers to physician practices, allowing physicians to readily access these services in their office setting. Case management can also be accessed through hospital social work or nursing departments or a local area agency on aging.

With the exception of private long-term care insurance, there is no third-party coverage for case management as a discrete service. Traditional Medicare programs do not cover case management services. Most TEFRA Medicare managed care programs will have case managers. Publicly funded services are available based on financial eligibility. For Medicaid recipients in many counties, these services are free. Private case management is also widely available, with costs ranging between $55 and $95 per hour.

Geriatric Assessment

Geriatric assessment is a multidisciplinary effort to address the medical, functional, social, and psychological needs of older people with multiple problems. These assessments usually include evaluations by workers in several disciplines such as medicine, nursing, and social work. Some assessment programs include occupational and physical therapy, pharmacy, and psychology. The goals of a geriatric assessment are to identify any treatable problems, to maximize patients' functional status, and to recommend the most effective care to achieve the best outcome. Most assessment services are targeted toward frail older persons living at home. There are assessment services specifically for patients with dementia. Most assessment services involve consultation only, although some provide follow-up care for a specified period of time.

Not all communities have geriatric assessment services. Many are associated with a geriatric department in university medical centers or with geriatric community programs. Some dementia-specific federally funded assessment services help in establishing diagnoses and developing treatment plans for patients with possible dementia.

Primary care physicians should consider a referral for geriatric assessment when they need a second opinion about a patient's problems, a change in a patient's domestic setting is being considered, or a substantial but unexplained change in a patient's functional or mental status has occurred.

More than a decade ago, remarkable benefits were reported from inpatient geriatric evaluations, including shorter hospital stays, improved functional status, and fewer medications.[2] Other evaluations of the benefits of geriatric assessment, however, have been contradictory. At the very least, as Campion has pointed out, "the physicians, nurses, family, and the patient may well see value in the way an experienced geriatrics team helps with complicated problems such as incontinence, confusion, immobility, and complex drug interactions."[3]

Geriatric assessment services are frequently covered by Medicare, particularly initial evaluations. As with other geriatric services, payment depends on the setting. For example, many assessment services for patients with dementia may be funded separately at a state or local level.

Adult Day Health Care

Adult day services provide a variety of facility-based rehabilitation and social and support services to functionally impaired persons. Patients typically attend such centers at least several days a week. There are an estimated 2,000 centers across the country serving more than 70,000 people. The major objectives of these programs are to provide an alternative to institutionalization, to increase functional abilities, and to provide respite for caregivers.[1]

Services vary depending on the center. Some day care centers are targeted to specific populations, such as those with psychiatric disorders, dementia, or developmental disabilities. Some centers provide care for each of these groups at the same site but with separate programming. Basic services include meals, transportation, personal care, and recreation. Many centers also include nursing, rehabilitation, social services, case management, and limited medical services such as podiatry. Some communities have comprehensive outpatient rehabilitation facilities that focus on rehabilitation. They provide a coordinated approach to outpatient rehabilitation that includes physical therapy, occupational therapy, social work, nursing, speech, and psychological services as needed.

The target population for this service includes patients who have one or more of the following conditions: impairment in activities of daily living such as eating, bathing and toileting; impairment in mobility, including those who are wheelchair-bound; and cognitive impairment due to developmental disability or dementia. Payment for day care services is usually on a sliding scale with the daily cost being about $50 per day. Medicaid covers these services in most communities.

Home Health Services

Home health care provides a variety of services that include skilled nursing, rehabilitation, social work, and personal care. The term "home health care" refers to the professional nursing, physical and occupational therapy, and social work services provided on a per-visit basis by a licensed certified agency. Typically, home health care is begun after a lengthy hospital stay and is limited to a specified period of time

Shortened hospital stays and managed care influences, however, have encouraged more flexible uses of home health care, such as following ambulatory surgery. Hospital discharge planners and case managers arrange post-hospital home care services, while physicians' offices can contact a home health agency directly from the primary care setting. Physicians' orders are required for all skilled services. Medicare, Medicaid, and private insurance cover skilled services as long as they are considered medically necessary.

Home care services include the personal care, homemaking, and chore services that are often the backbone of long-term care in the home. Assistance with bathing, grooming, dressing, meals, and housekeeping for a few hours a day can make the difference between staying in the community or going to a nursing home. Yet, this sector of home care is not reimbursed by Medicare or private insurance except under limited circumstances. Unless patients are eligible for Medicaid, they and their familes pay for these services themselves. Home care workers can be hired privately or through a home care agency. Although agency charges are more expensive, the agency handles all screening, hiring, training, supervision, and replacement of the workers.[4]

It is estimated that at least 11 million people of all ages use home care. There are at least 15,000 agencies in the United States providing these services. Agencies may be independent or affiliated with a hospital or managed care group.[4] Independent agencies can be located by contacting the local area agencies on aging.

Program for All-inclusive Care for the Elderly

The Program for All-inclusive Care for the Elderly (PACE) is a Medicare or Medicaid managed care capitated program that integrates primary medical care, social day care, home care, and rehabilitation into one integrated system. Currently there are 11 cities with fully developed PACE sites. Another 8 cities have programs in development, and 31 organizations are doing feasibility studies for the development of a PACE site.[5,6]

To be eligible for this program, a patient must meet nursing home admission criteria. The goal is to keep frail older persons living at home—out of nursing homes and out of hospitals. Evaluation of these services has shown decreased time in the hospital and high client and family satisfaction. Further quality review of these services is being done. Many managed care organizations are beginning to look at this model for possible incorporation into their services for their more at-risk patients.

Who Should Be Referred to Services?

Who should be referred to these services is not always clear. A number of studies have attempted to answer this question by evaluating the targeting criteria—that is, identifying which subgroups of the elderly are most likely to benefit from a service. Some of the criteria identified are dependency in two or more activities of daily living, no family support, dementia, multiple chronic diseases, and repeat hospital stays. If patients do not meet the criteria, the efficacy of any of the geriatric services is questionable.[7]

More recently, an attempt has been made to evaluate those people at risk in Medicare managed care programs. This instrument, the "probability of repeated admissions," consists of eight close-ended questions that can be asked by mail or by telephone. These questions focus on patients' self-report of health, recent hospital admissions, and social support.[8–11]

For community physicians, however, patients who might benefit from increased services include those meeting the targeting criteria but may also include patients who may need more than basic medical interventions and those who are being considered for nursing home placement. Patients with dementia, poor functional status, and weak social support systems are also good candidates for these community services.

Financing of Services

Financing varies for these services, depending on patients' financial status and individual health insurance. Many of the services are covered by Medicaid, including case management, day care, and home care, although some restrictions may apply. Day care is covered by many Medicaid programs, but not by Medicare. Medicare does, however, cover comprehensive outpatient rehabilitation services because these are seen as short-term services.[12]

Most middle-income people do not have insurance that covers these services and usually have to pay for them themselves. As mentioned, Medicare will cover short-term homecare, usually after a long-term hospital stay, but will not finance long-term personal care unless there is a specific skilled-nursing need attached to the service.

Efficacy of Services

Many studies have focused on the effectiveness of the above services, with varying conclusions.[13–20] A meta-analysis tended to show improvement in selected aspects of medical care.[13] These improvements included increased identification of unrecognized medical and psychosocial problems, reduced medications, improved functional status, fewer hospital stays, and increased

survival. The effectiveness studies have been hampered, however, by the diversity of the assessment programs, the differences of the populations studied, and the type of data collected.

The PACE data suggest that this managed care model shortened hospital stays and decreased nursing home care, which may reflect a cost savings. Comparisons with other programs are difficult to assess, however, because of the complex nature of the PACE progams.[5, 6]

A literature review was done of 32 studies of community-based, long-term-care programs that included home care, ADIC, and other coordinated packages of services.[20] In almost all cases, these services did not increase survival and did not enhance or slow the rate of deterioration of functional status. There was a tendency for higher client and caregiver satisfaction, although this tended to decrease if the services extended beyond a certain time. Cost-effectiveness is still not adequately evaluated.

Conclusion

Many communities now have an array of geriatric community services available to physicians. The goal of these services is to help patients achieve the greatest degree of functional ability and independence. Although data on outcomes are highly varied, these services can be a valuable adjunct to the care of targeted frail older persons. In addition to private physicians and social service agencies, managed care organizations are using these services, particularly case management for their high-risk clients. Physicians can benefit from these services in the following ways:

- By increased information on patients' functional and psychosocial status through geriatric assessment.
- By assistance in directing their patients to useful community resources through case managers.
- By increasing patient and family satisfaction with their current health care.

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SUCCESSFUL AGING

Preventing Decline in Function
Evidence from Randomized Trials Around the World

EDWARD H. WAGNER, MD, MPH, *Seattle, Washington*

Over the past decade, increasing epidemiologic evidence points to a few important risk factors for loss of mobility and functional decline, such as inactivity, cigarette smoking, obesity, depression, and alcohol and drug misuse. Global interventions addressing these risk factors along with other medical problems have been evaluated in randomized controlled clinical trials. With few exceptions, these trials have shown that intervention has a positive effect on health and functional status, as well as reducing length of stay in a hospital or nursing home. The extent to which the success of these programs is attributable to risk-factor reduction or to geriatric assessment and management is uncertain.

(Wagner EH. Preventing decline in function: evidence from randomized trials around the world. In: Successful Aging. West J Med 1997; 167:295–298)

Successful aging, in this issue of THE WESTERN JOURNAL OF MEDICINE, has been defined as the maintenance of a high-quality, independent life. To maintain independence and full function it is essential to prevent the loss of physiologic capacity and reserves, a condition commonly referred to as frailty.[1] The maintenance of function and quality of life depends on having sufficient cardiovascular, neurologic, sensory, and musculoskeletal reserves to withstand the stresses of everyday life, whether trivial (such as negotiating an uneven pavement) or profound (acute illness or loss of a loved one). Good mental health is an important effect modifier; that is, persons at a given level of physiologic stamina will be less disabled by stress if psychosocially healthy. Many of the most common, and most devastating, problems associated with advanced age are, in fact, related to frailty, not necessarily to aging per se. For example, in a study of the predictors of major geriatric syndromes (falls, incontinence, and functional dependence) among a cohort of seniors living in an adult community, each of these three seemingly unconnected syndromes was associated with a common group of risk factors.[2] These risk factors—leg weakness, arm weakness, reduced vision or hearing, and anxiety— are all closely related to frailty.

If frailty is a major determinant of unsuccessful aging, what are its predictors, and are they preventable? The risk factors for frailty, as defined by loss of function, loss of mobility, and the propensity to fall, have received considerable study over the past 10 to 15 years. These studies have the same basic structure: large cohorts of older adults are identified, queried, and examined to establish a baseline, then observed for a number of years with periodic evaluations of health and function. Recently these studies have been carefully reviewed.[3,4] In addition to chronic diseases like stroke or osteoarthritis of the knee, future disability is most likely to befall those who are inactive, smoking, depressed, or obese. Other risk factors found to be predictive in some studies include alcohol abuse, psychotropic drug use, malnutrition, vision or hearing deficits, and home safety hazards. With a few obvious exceptions, we now have reasonably successful intervention modalities for each of these risk factors.

Multicomponent Preventive Interventions

Over the past decade or so, investigators in western Europe and Canada have designed and tested complex intervention strategies to prevent loss of independence, institutionalization, and mortality in community-dwelling older adults. These interventions have relied primarily on home visits by nurses, nurse practitioners, or, occasionally, nonprofessional volunteers. The

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emphasis of these interventions has been on identifying unrecognized social isolation, functional deficits, and medical problems and to respond to these with advice and referrals to medical and social services. At least eight such programs have been tested in randomized trials and reported in the literature.[5–12] Nearly all have reported a variety of benefits to the study participants receiving intervention at the end of the follow-up period, including reduced rates of institutionalization, hospital admissions, and death. Few of these studies reported evaluations of activities of daily living or included self-reported health status; those that did found few differences.[12]

These home-based interventions have often included "health education" or "advice," but the content was rarely specified. It is therefore unclear whether these educational efforts were directed at risk factors for disability. Instead, the reports of these interventions emphasize assessment of function followed by advice and referral to deal with medical or social problems. Risk factors for disability or falls are not mentioned explicitly, and efforts to change behavior (such as physical activity) are not often mentioned.

A similar program was tried in an American context.[3] A home-visit strategy included a focus on risk factors for disability such as smoking, poor nutrition, and lack of exercise or home safety. In this study, 254 war veterans were randomly assigned to receive or not to receive an in-home preventive assessment program. The comprehensive assessment, performed by a physician assistant or research nurse, included a medical history, a focused physical examination, a health behavior questionnaire, home safety inspection, gait and balance evaluation, and blood tests. Findings were discussed with a geriatrician, and the resulting recommendations were summarized in letters to patients in which the patients were also encouraged to share these recommendations with their physician. In addition, patients were visited at four-month intervals by trained volunteers to assist patients in implementing the recommendations. The vast majority of recommendations were for follow-up medical or dental evaluations, immunizations, or changes in lifestyle (diet, exercise, smoking, alcohol, and home safety). At 12 months, patients who were the targets of this intervention strategy had significantly higher rates of immunization and on average had no decline in instrumental activities of daily living; the activities of control subjects, in contrast, declined substantially.

A somewhat similar in-home assessment and intervention program was studied in a randomized trial involving 414 community-dwelling seniors aged 75 or older.[14] The assessment and follow-up interventions, conducted by gerontologic nurse practitioners (GNPs), resembled those of the study described earlier,[13] except that the GNPs maintained quarterly follow-up over three years. The subjects' personal physician was contacted only if necessary. Most recommendations involved self-care: exercise, nutrition, and sleep. After three years, program participants were significantly less likely than controls to lose independence in instrumental activities of daily living (12% versus 22%, $p = 0.02$) or to require permanent nursing home placement (4% versus 10%, $p = 0.02$).

Our research group has developed and tested disability and fall prevention programs conducted in community settings (primary care clinics, senior centers),[15,16] all of which involve risk factor assessment, discussion of risk factors, development of a prevention plan, and follow-up intervention for those found to be at risk. The risk factors given priority have changed over time, but have always included inactivity, symptoms of depression, polypharmacy (excessive use of prescription drugs), home safety hazards, and alcohol abuse.

In our first study, a randomized controlled clinical trial involving 1,559 senior health management organization enrollees, the risk factors to be determined by questionnaire and medication review included inactivity, alcohol abuse, polypharmacy, uncorrected vision and hearing deficits, symptoms of depression, and home safety hazards.[16] Interventions included brief instructional courses such as a two-hour orientation to exercise for those who were sedentary and classes for those with uncorrectable hearing deficits, distribution of pamphlets, recommendations by pharmacists for changes in medication (both to patients and to physicians), and occasional referrals for evaluation and treatment of such conditions as major depression or undiagnosed hearing loss. After the initial visit, follow-up was limited to telephone calls from the nurse. After a year, the intervention group had about half the incidence of significant functional decline experienced by controls (7% versus 13% of controls) and about two thirds of the incidence of falls (27% versus 37% of controls). These positive effects disappeared after two years, probably because interventions were limited to the first year of the study.

In our next study, a randomized pilot study for a larger evaluation of a senior center–based disability and fall prevention program, we enhanced our intervention efforts by adding a thrice-weekly supervised exercise program to the nurse assessment and treatment of risk factors.[15] The risk factors (again determined largely by questionnaire) now included cigarette smoking and poor nutrition in addition to those previously mentioned. Nurse follow-up was a defined set of two to eight telephone calls at intervals over the following year. The six-month exercise program involved groups of 10 to 15 seniors meeting three times a week at their local senior center with a trained exercise instructor. Each 60-minute session included warm-up and balance exercises, 15 to 20 minutes of strength training using cuff weights, 20 minutes of brisk walking, and a cool-down period featuring flexibility training. At the end of six months, the 53 seniors randomly assigned to the intervention group had significant improvements in functional status and declines in symptoms of depression compared with controls. These improvements in self-reported function and mental health were accompanied by significant improvements in physical performance as measured by endurance, strength, and balance tests. This intervention

strategy is now being tested in a randomized trial involving a larger and more ethnically and socioeconomically diverse senior population. The magnitude of the effect on self-reported physical function in this trial was much higher than that seen in our previous trial. We attribute this to the increased emphasis given to the exercise component of the intervention.

Features of Successful Programs

The studies cited earlier generally demonstrate that systematic interventions involving assessments and interventions that address functional status and known risk factors for disability result in reductions in disability and help participants maintain independence. These programs share many common features, but also differ in important ways.

Subjects

The subjects in these randomized controlled trials ranged from seniors requiring long-term care services to ambulatory older adults with no difficulty with activities of daily living. Although there is some evidence that assessment and referral interventions are more effective with less healthy seniors, the evidence to date suggests that relatively healthy seniors also benefit from prevention-oriented interventions.

Assessment

Essentially all senior prevention interventions begin with assessments, but these vary widely in their content, extent, and objectives. The studies conducted to date do not allow an estimate of the relative importance of changes in health practices, on the one hand, and identification and management of clinical problems on the other. If much of the effect of intervention is related to changes in health practices, then the assessment can be limited to the measurement of known risk factors. If it is largely attributable to the identification and treatment of illness, a more extensive clinical evaluation is required. Because interventions that emphasize risk factor reduction have proved to be effective, more limited clinical evaluation may be justified.

Personal Attention

The intervention strategies reported in the aforementioned studies all include one-on-one contact and communication between an older subject and a caregiver. They are also tailored to the individual needs of each participant. Although there is evidence to suggest that successful aging intervention can be provided in group settings,[17] the opportunity for one-on-one contact and communication would seem to be a valuable component of an effective intervention strategy.

Intervention

All of the intervention programs described earlier offer clinical evaluation and referral as well as health education directed at personal behavior; what differs is the apparent balance between the two. The trials conducted in southern California, presumably because of their close links with clinical geriatrics programs in that area, included a relatively predominant emphasis on clinical evaluation compared with health education. The Seattle interventions, on the other hand, emphasized behavioral risk factors, particularly those pertaining to physical activity, and involved relatively little clinical evaluation. Case findings were largely limited to assessments for hypertension and depression. Few studies have described in detail the nature and content of the health advice or education offered or the extent to which the nurses were prepared to provide support to participants attempting to make major changes in behavior.

The availability of supervised exercise programs that include strength and balance training may greatly enhance the effectiveness of preventive interventions. Physical activity is probably the single most important feature of successful aging because it prevents or at least slows the physiologic decline associated with frailty.[18] More focused randomized trials have demonstrated the ability of supervised exercise programs to increase the functional status of the full range of older adults, including socially active younger seniors,[16] institutionalized nonagenarians,[19] and those suffering from arthritis.[20] Evidence is also mounting that physical activity prevents falls,[21] and research in this area points to the importance of including strength and balance training along with walking or other endurance activities in senior exercise programs. The importance of a multidimensional senior exercise program and the difficulties most of us have maintaining regular exercise regimens may explain why almost all reported successful physical activity interventions have included considerable supervision.

Caregivers and Venues

Most interventional care provided thus far has been given by a nurse. The need for a trained clinician (for example, a physician assistant or nurse practitioner) seems to depend primarily on the degree of emphasis given by the program to clinical assessment. Home visits by nonprofessional volunteers have also been tried—safely, it seems, but with mixed results. In our experience, the choice of caregiver should be determined by the subject's medical condition. Frailer seniors, with more severe or persistent medical problems, may need a more clinically trained provider (for example, a geriatric nurse practitioner) to oversee their preventive program and balance their preventive and therapeutic needs. The degree to which a primary care physician is involved varies. Although it is possible to achieve positive effects with minimal involvement on the part of the patients' personal physicians,[14] the best intervention programs are those in which primary medical care is an integral part of the regimen.

Except for the Seattle studies, in which the interventions were provided in primary care clinics[15] or in community senior centers,[16] all interventions took place in

the seniors' homes. Home-based interventions are more expensive than those provided in public institutions, but they have the obvious advantage of convenience for patients, while giving caregivers the opportunity for a more informed assessment of the person's environment and living conditions. Although we conducted our first preventive intervention study in primary care clinics, senior centers offer distinct advantages, if they have sufficient space, because of the low-cost intervention opportunities provided by their array of social and health programs, the supportive social environment, and the availability of volunteer assistance.

Sustained Follow-up

Consideration of these randomized controlled trials highlights the critical importance of regular follow-up evaluation. Our first trial demonstrated that improvements dissipate if the intervention is short-lived.[15] Several of the studies continued the intervention for three years, and these longer interventions appeared to achieve more positive effects. Subjects tended to be visited or otherwise contacted three to six times per year. We have recently reviewed the literature on the self-management of chronic illness[22] and found that sustained follow-up over months and years is a characteristic of programs that have proved successful in changing behaviors and improving disease outcomes. There is now mounting evidence that such follow-up can be conducted largely by telephone.[23,24]

Conclusion

To date, most multicomponent interventions to maintain function and independence in older populations have combined geriatric assessment and management with disability and fall prevention. Future research should attempt to disentangle the relative contributions of these two components. Doing so will help caregivers select the right subjects and design cost-effective programs. Until definitive results are in, the available evidence suggests that health care professionals should ensure that their older patients receive systematic attention to their functional status and the risk factors for disability to which this population is prone.

The intensive program described by Stuck and colleagues,[14] which involved extensive assessments and physician referrals by nurse practitioners, was estimated to cost approximately $660 per subject per year ($480 in direct costs and $180 in added physician visits), while saving $420 per subject per year in nursing home costs. A less intensive program that emphasized environmental and behavior change should cost the health system a fraction of that amount, without resulting in increased physician visits. In light of the fact that the average Medicare recipient accumulates $4,000 to $5,000 per year in health care costs, such programs would appear to represent wise investments and important medical advances in helping seniors age successfully.

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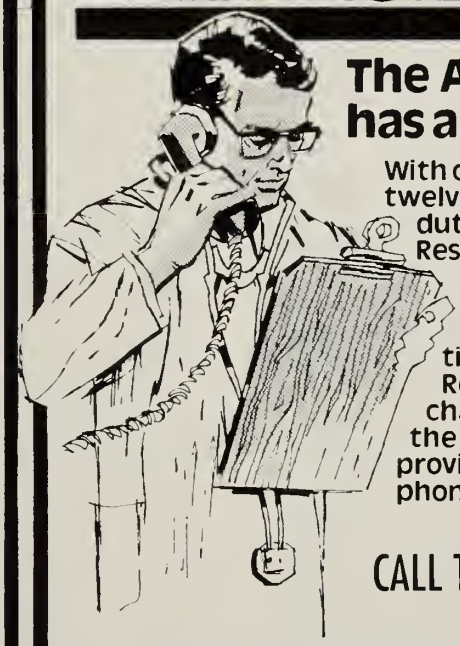

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In accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (URM), 1997

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3. Cancer in South Africa [editorial]. S Afr Med J 1994; 84(12):15

Books

4. Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996 [author of book is same as author of chapter]

5. Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995, pp 465–478 [authors of book differ from chapter author]

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6. Shusterman D. Espresso maker's wrist [correspondence]. West J Med 1990; 152:721–722

Scientific or Technical Report

Issued by funding or sponsoring agency:

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Issued by performing agency:

8. Field MJ, Tranquada RE, Feasley JC, editors. Health services research: work force and educational issues. Washington DC: National Academy Press; 1995. Contract No.: AHCPR282942008. Sponsored by the Agency for Health Care Policy and Research

9. Centers for Disease Control and Prevention. Recommendations and Reports: 1997 Revised guidelines for performing CD4+ T-cell determinations in persons infected with human immunodeficiency virus (HIV) MMWR 1997; 46(Jan 10):RR-2

Proceedings

10. Kimura J, Shibasaki H, editors. Recent advances in clinical neurophysiology. Proceedings of the 10th International Congress of EMG and Clinical Neurophysiology; 1995 Oct 15–19; Kyoto, Japan. Amsterdam: Elsevier; 1996

Mass Circulation Publications

11. Lee G. Hospitalizations tied to ozone pollution: study estimates 50,000 admissions annually. The Washington Post 1996 Jun 21; Sect A:3 (col 5)

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Continued on page 192

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12. Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

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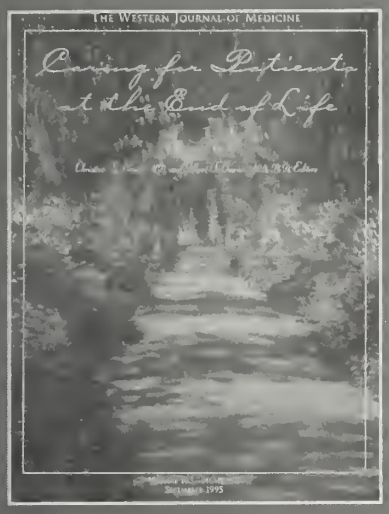

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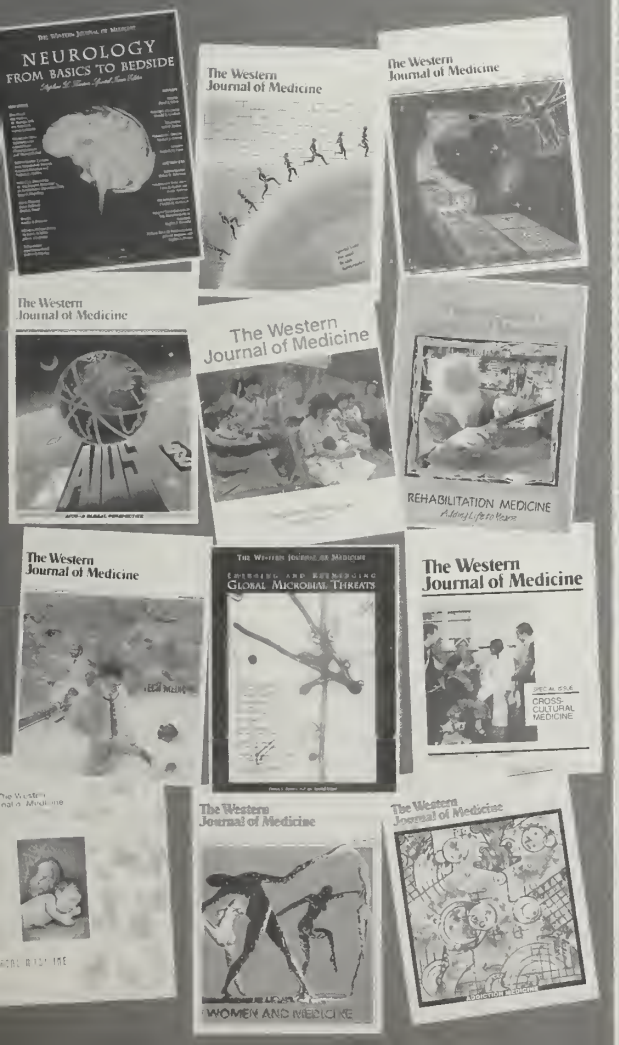

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VOLUME 167 • NUMBER 5 NOVEMBER 1997

NOV 21 1997

ARTICLES

315 AIDS-Related Disseminated Histoplasmosis in San Francisco, California
D N FREDRICKS, N ROJANASTHIEN, and M A JACOBSON

322 Intramuscular High-Dose Triamcinolone Acetonide in the Treatment of Severe Chronic Asthma
L MANCINELLI, L NAVARRO, and O P SHARMA

330 Geographic Distribution, Supply, and Need for Generalist Physicians in Alaska
D R JOHNSON and T E NORRIS

336 Closer to Home (or Home Alone?)—The British Columbia Long-Term Care System in Transition
B L BRODY, H J SIMON, and K L STADLER

EPITOMES

343 Important Advances in Allergy and Immunology

ALERTS, NOTICES, AND CASE REPORTS

351 Paralytic Shellfish Poisoning in Kodiak, Alaska
B D GESSNER, J P MIDDAUGH, and G J DOUCETTE

353 Resolution of Propylthiouracil-Induced Hepatic Failure After Treatment of Thyrotoxicosis
W KHOVIDHUNKIT, and R V FARESE

356 Trimethoprim-Sulfamethoxazole Associated With Hyperkalemia
M MARINELLA

EDITORIAL

359 Treatment of Chronic Severe Asthma
H BOUSHEY

SPECIAL SERIES—PART I

361 A Few Words About *The Quest for Mercy*
L H CLEVER

362 The Quest for Mercy—The Forgotten Ingredient in Health Care Reform
R BULGER

OTHER FEATURES

305 Subscription Information

309 Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming

374 Classified Advertising

Detailed Table of Contents: 307, 308

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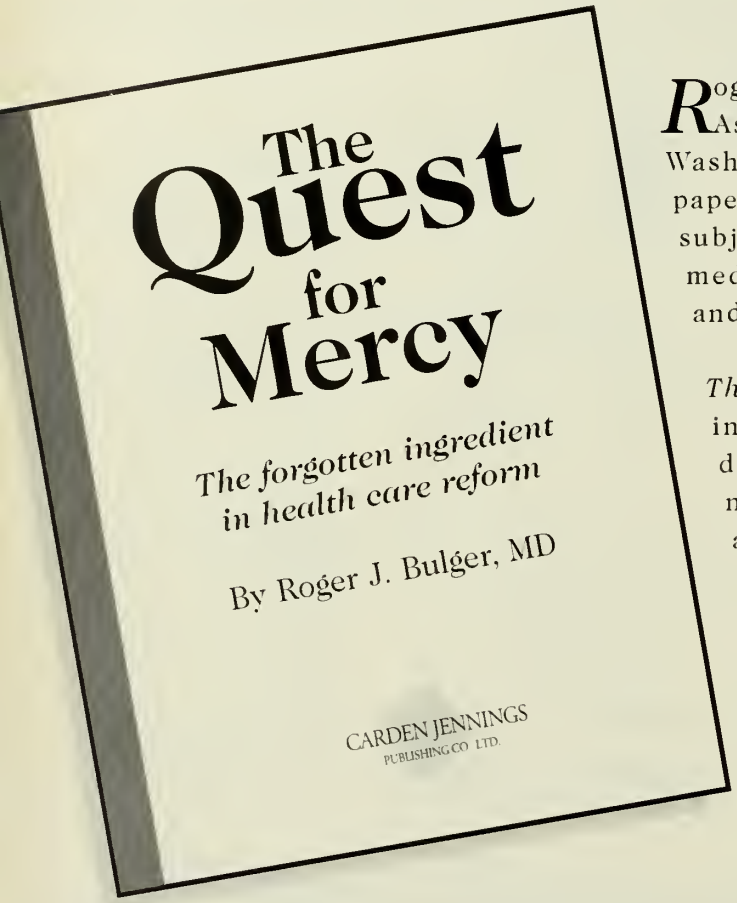

Roger J. Bulger, MD, FACP is President of the Association of Academic Health Centers in Washington, DC. He has published scores of papers and chapters, as well as three books on subjects ranging from infectious diseases to medical education, humanities, Hippocrates, and, of course, academic health centers.

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CONTENTS

ARTICLES

315 **AIDS-Related Disseminated Histoplasmosis in San Francisco, California**

DAVID N. FREDRICKS, MD; NOPPAMAS ROJANASTHIEN, MD; and MARK A. JACOBSON, MD

From the Division of Infectious Diseases and Geographic Medicine, Stanford University Medical Center, Stanford; Department of Pharmacology, Chiang Mai University, Chiang Mai, Thailand; and Department of Medicine, University of California, San Francisco, and the Medical Service, San Francisco General Hospital and Medical Center.

322 **Intramuscular High-Dose Triamcinolone Acetonide in the Treatment of Severe Chronic Asthma**

LAVIERO MANCINELLI, PharmD; LETTE NAVARRO, RNP; and OM P. SHARMA, MD

From the Division of Pulmonary/Critical Care Medicine, University of Southern California, School of Medicine, Los Angeles.

330 **Geographic Distribution, Supply, and Need for Generalist Physicians in Alaska**

DEANNA R. JOHNSON and THOMAS E. NORRIS, MD

From the University of Washington School of Medicine, Seattle.

336 **Closer to Home (or Home Alone?)—The British Columbia Long-Term Care System in Transition**

BARBARA L. BRODY, MPH; HAROLD J. SIMON, MD, PhD; and KATHLEEN L. STADLER

From the Division of International Health and Cross-Cultural Medicine, Department of Family and Preventive Medicine, University of California, San Diego School of Medicine, La Jolla.

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Allergy and Immunology

Items of progress in allergy and immunology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance.

343 **Recommendations for Immunizations in HIV-Infected Individuals**

DIANA MARQUARDT, MD

344 **Drug Reactions in HIV/AIDS**

HAMID HUSSAIN, MD; GILDON BEALL, MD; and MARGERY SANWO, MD

344 **Latex Allergy—The Latest Insights**

KENNETH KIM, MD

345 **Antileukotrienes—1997 and Beyond**

SHELDON L. SPECTOR, MD

346 **Combination Therapy for HIV Disease**

ROBERT J. FRASCINO, MD

347 **Advances in Allergic Rhinitis Pharmacotherapy**

MICHAEL J. WELCH, MD

348 **Treatment of Chronic Urticaria**
ALLEN KAPLAN, MD

348 **Inhaled Corticosteroids for Asthma Therapy**
LEWIS KANTER, MD

349 **Intravenous Immune Globulin in Neuromuscular Disorders**
SUDHIR GUPTA, MD

ALERTS, NOTICES, AND CASE REPORTS

351 **Paralytic Shellfish Poisoning in Kodiak, Alaska**
BRADFORD D. GESSNER, MD; JOHN P. MIDDAUGH, MD; and GREGORY J. DOUCETTE, PhD
From the Alaska Division of Public Health, Anchorage; and the United States Department of Commerce, National Oceanic and Atmospheric Administration, National Marine Fisheries Service, Southeast Fisheries Science Center, Charleston.

353 **Resolution of Propylthiouracil-Induced Hepatic Failure After Treatment of Thyrotoxicosis**
WEERAPAN KHOVIDHUNKIT, MD and ROBERT V. FARESE, JR., MD
From the Division of Endocrinology and Metabolism, Department of Medicine, and the Gladstone Institute of Cardiovascular Disease, University of California, San Francisco.

356 **Trimethoprim-Sulfamethoxazole Associated With Hyperkalemia**
MARK A. MARINELLA, MD
From the Department of Internal Medicine, Wright State University School of Medicine, Dayton.

EDITORIAL

359 **Treatment of Chronic Severe Asthma**
HOMER A. BOUSHEY, MD
From the University of California, San Francisco.

SPECIAL SERIES

361 **A Few Words About *The Quest for Mercy***
LINDA HAWES CLEVER, MD

362 **Part I—The Quest for Mercy—The Forgotten Ingredient in Health Care Reform**
ROGER J. BULGER, MD

OTHER FEATURES

305 WJM Subscription Information

309 Continuing Medical Education Activities

374 Classified Advertising

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

Continuing Medical Education

ARIZONA • CALIFORNIA, HAWAII, NEVADA • COLORADO • IDAHO • NEW MEXICO • UTAH • WASHINGTON • WYOMING

ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale. (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (520) 626-7832; (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Paulette Richardson, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-3387. For more information on accreditation or certification, please write to the above address.

ALLERGY

January 18–23, 1998—**36th Annual Scientific Session of The Western Society of Allergy and Immunology.** Four Seasons Resort, Wailea in Maui, Hawaii. For more information contact Rebecca Gough, Exec. Administrator, PO Box 1122, Roanoke, Texas, 76262; (817) 491-2616, Fax (817) 491-2241.

ANESTHESIOLOGY

January 7–10, 1998—**UCSD Anesthesiology Update 1998.** UCSD at Hotel del Coronado, San Diego. Wed.–Sat. 18 hrs. Contact: Carol Heil (619) 543-2188.

May 17–22, 1998—**UCSD Anesthesiology Review Course.** UCSD at La Jolla Marriott, San Diego. Sun.–Fri. 37.5 hrs. $600. Contact: Carol Heil (619) 543-5202.

CARDIOLOGY

December 12–14—**15th Annual Advances in Heart Disease.** American College of Cardiology at Grand Hyatt on Union Square San Francisco. Fri.–Sun. 16 hrs. Contact: ACC Registration Secretary, Extramural Programs Dept., (800) 253-4636, ext. 695.

January 16–17, 1998—**Radiotherapy to Reduce Restenosis.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri.–Sat. 16.5 hrs. Contact: Laurel Steigerwald, Scripps Clinic Dept. Academic Affairs 403c, 10666 N. Torrey Pines Road, La Jolla, 92037 (619) 554-8556.

January 24, 1998—**Heart Failure.** Ritz-Carlton Huntington Hotel, Pasadena. Sat. 5 hrs. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

January 30–February 1, 1998—**Clinical Nuclear Cardiology: Case Review With the Experts.** American College of Cardiology at Cedars-Sinai Medical Center, Los Angeles. Fri.–Sun. 19 hrs. Contact: ACC Registration Secretary, Extramural Programs Dept., (800) 253-4636, ext. 695.

February 19–21, 1998—**Cardiovascular Health: Coming Together for the 21st Century.** UCSF at Hyatt Regency Embarcadero San Francisco. Thurs.–Sat. Contact: UCSF.

May 7–9, 1998—**8th Annual Symposium on Coronary Stenting.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs.–Sat. Contact: Laurel Steigerwald, Scripps Clinic (619) 554-8556.

COMPUTER TECHNOLOGY

December 11–13—**Computer Training for Physicians.** UCSD at National University San Diego. Thurs.–Sat. 18 hrs. $575. Contact: OCME (619) 534-3940.

January 28–31, 1998—**Medicine Meets Virtual Reality: Art, Science, Healthcare Evolution.** UCSD at San Diego Hyatt Regency. Wed.–Sat. Contact: Karen Morgan (760) 751-8841.

DERMATOLOGY

January 15–18, 1998—**Practical Dermatology for the Primary Care Physician.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency La Jolla, San Diego. Method, AV, L, SB, W. $575. Thurs.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

January 31–February 1—**Melanoma 1998: 8th Annual Cutaneous Malignancy Update.** Scripps Clinic at Scripps Memorial Hospital, La Jolla. Sat.–Sun. 11.5 hrs. Contact: Jill Hofmans, Scripps Clinic, (619) 554-8556.

May 3–6, 1998—**Practical Dermatology for the Primary Care Physician.** Las Vegas. Sponsored by Continuing Medical Education Associates. Caesar's Palace Las Vegas. Method, AV, L, SB, W. $575. Sun.–Wed. 20 hrs. credit: AMA, AOA, AAP, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

EMERGENCY MEDICINE

December 15–19—**Emergency Medicine Symposium II.** UCSD at UCSD San Diego. Mon.–Fri. 32 hrs. $495. Contact: OCME (619) 534-3940.

February 27–March 3, 1998—**Critical Care Medicine.** Las Vegas Hilton Hotel, Las Vegas. Fri.–Tues. 26 hrs. Cost: $785/MD, $585/Allied Health. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

February 16–20, 1998—**Emergency Medicine Symposium I.** UCSD at La Jolla Marriott San Diego. $495. Mon.–Fri. 32 hrs. Contact: OCME (619) 534-3940.

March 25–27, 1998—**14th Annual Advances in Emergency Medicine.** UCSF at Radisson Miyako Hotel, San Francisco. Wed.–Fri. 17 hrs. $520. Contact: UCSF (415)476-5208.

April 20–24, 1998—**Emergency Medicine Symposium III.** UCSD at La Jolla Marriott, San Diego. Mon.–Fri. 32 hrs. $495. Contact: OCME (619) 534-3940.

May 11–15, 1998—**Emergency Medicine Symposium.** UCSD at La Jolla Marriott, San Diego. Mon.–Fri. 16 hrs. $225. Contact: OCME (619) 534-3940.

May 15–16, 1998—**Trauma/Critical Care.** Ritz-Carlton Huntington Hotel, Pasadena. Mon.–Tues. 14 hrs. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

May 13–16—**Semiannual Wound Management Workshop.** UCSD at La Jolla Marriott, San Diego. Wed.–Sat. 15 hrs. $475. Contact: Edith Bookstein (619) 454-3212.

ENDOCRINOLOGY

March 5, 1998—**Diabetes Update.** UCSF at Radisson Miyako Hotel, San Francisco. Thurs. 7.5 hrs. $195. Contact: UCSF (415)476-5208.

March 6–7, 1998—**Advances in Endocrinology and Metabolism.** UCSF at Radisson Miyako Hotel, San Francisco. Fri.–Sat. 11 hrs. $310. Contact: UCSF (415)476-5208.

FAMILY PRACTICE/PRIMARY CARE

December 4–5—**Controversies in Women's Health.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs.–Fri. 13 hrs. $355. Contact: UCSF (415) 476-5208.

December 6—**Management of Type 2 Diabetes.** Sheraton Grande Hotel, Los Angeles. Sun. 5.5 hrs. $35. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

January 15–18, 1998—**Practical Dermatology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Regency, La Jolla. Thurs.–Sun. 20 hrs. $575. Contact: Victoria Gonzales (800)993-2632.

April 9–10, 1998—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** Stanford Court Hotel, San Francisco. 14 hrs. $375 ($425 if postmarked after February 26). Contact: Program Coordinator, Dept. of Family and Community Medicine, UCSF School of Medicine, 500 Parnassus Ave., MU-3E, San Francisco 94143-0900. (415) 476-5250.

February 5–6, 1998—**Clinical Allergy and Immunology for Primary Care Family Physicians.** UCSF at Radisson Miyako Hotel, San Francisco. Thurs.–Fri. 7.5 hrs. $125. Contact: UCSF (415)476-5208.

February 12–15, 1998—**Office Gynecology and Women's Health for the Primary Care Physician.** UCSF at Hyatt Islandia, San Diego. Thurs.–Sun. 20 hrs. $575. Contact: Victoria Gonzales (800)993-2632.

March 14, 1998—**Gastroenterology and Hematology Update for the Primary Care Physician and Hands-On Flexible Sigmoidoscopy Workshop.** UC Davis at Cancer Center Auditorium, Sacramento. Sat. 6 hrs. $105. Contact: UCD (917)734-5390.

April 18, 1998—**Cardiology for the Primary Care Physician.** UC Davis at UCDMC Cancer Center Auditorium, Sacramento. Sat. Contact: (916) 734-7203.

April 23–26, 1998—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Regency, San Francisco. Thurs.–Sun. 20 hrs. $575. Contact: Victoria Gonzales (800) 993-2632.

May 15–19, 1998—**Primary Care Essentials.** San Francisco. Sponsored by Continuing Medical Education Associates. Grand Hyatt on Union Square San Francisco. Method, AV, L, SB, W. $750. Fri.–Tues. 32 hrs. credit: AMA, AOA, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

July 6–9, 1998—**Family Practice Board Review Course.** Fairmont Hotel, San Francisco. 25 hrs. $475 ($525 if postmarked after May 25). Contact: Program Coordinator, Dept. of Family and Community Medicine, UCSF School of Medicine, 500 Parnassus Ave., MU-3E, San Francisco 94143-0900. (415) 476-5250.

GERIATRICS

May 7–8, 1998—**Latest Advances in Alzheimer's Disease.** UCSD at San Diego. Thurs.–Fri. 16 hrs. $225. Contact: Phyllis Lessin/Joyce Zilner (619) 662-5800.

INFECTIOUS DISEASE

December 3—**AIDS-Associated Malignancies.** UCSF at Palace Hotel, San Francisco. Wed. 4.5 hrs. Contact: UCSF (415) 476-5208.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Education Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education, (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

February 6–7, 1998—**16th Annual Infectious Disease Conference.** UC Davis Medical Center at Sacramento Hilton Inn. Fri.–Sat. Contact: (917) 734-5390.

February 19–21, 1998—**Epidemiology and Prevention of Infectious Diseases.** UCSF at Grand Hyatt on Union Square, San Francisco. Thurs.–Sat. Contact: UCSF (415) 476-5208.

May 6–9, 1998—**19th Annual Advances in Infectious Diseases.** UCSF at Palace Hotel, San Francisco. Wed.–Sat. 17.5 hrs. $430. Contact: UCSF (415) 476-5208.

INTERNAL MEDICINE

March 7–14, 1998—**Diagnostic & Therapeutic Skills in Internal Medicine.** Mauna Kea Beach Hotel, Kameula, HI. Mon.–Fri. 27 hrs. $635. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

March 20–26, 1998—**Internal Medicine 1998.** San Diego. Sponsored by Continuing Medical Education Associates. Hotel del Coronado San Diego. Method, AV, L, SB, W. $795. Fri.–Thurs. 45 hrs. credit: AMA, AOA, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

April 2–5, 1998—**1998 Annual Session American College of Physicians.** ACP at San Diego Convention Center. Wed.–Sun. 29 hrs. Contact: ACP Customer Service (800) 523-1546 ext. 2600.

April 4, 1998—**New Treatments in Chronic Liver Disease.** Scripps Clinic at Scripps Clinic, La Jolla. Fri 6 hrs. Contact: Laurie A. Regis (619) 554-8556.

May 18–22, 1998—**26th Annual Advances in Internal Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon.–Thurs. 33.5 hrs. Contact: UCSF (415) 476-5208.

NEPHROLOGY

January 29–31, 1998—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at La Jolla Marriott. Thurs.–Sat. 17 hrs. $425.

NEUROLOGY

December 6—**Movement Disorders.** Hotel Sofitel, Los Angeles. Sat. 5.25 hrs. $25. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

January 31, 1998—**UCLA Neurology: Update for Primary Care Physicians.** Miramar Sheraton Hotel Santa Monica. 6 hrs. Contact: Sheryl Crowley, Office of Continuing Medical Education, 10920 Wilshire Blvd., Los Angeles 90024-6512 (310) 794-2620; Fax (310) 794-2624..

February 11–13, 1998—**Recent Advances in Neurology.** UCSF at Fairmont Hotel San Francisco. Wed.–Fri. 15 hrs. Contact: UCSF (415) 476-4251.

March 20, 1998—**STROKE: Van Der Meulen Symposium in Clinical Science.** USC Health Sciences Campus, Los Angeles. Fri. 7 hrs. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

NEUROSURGERY

January 16–18, 1998—**California Association of Neurological Surgeons Annual Session.** Parc Fifty Five Hotel, San Francisco. 7 hrs. Contact: Janine Tash, 5380 Elvas Ave., Ste. 216, Sacramento 95819, (916) 457-2267, fax (916) 457-8202.

OB/GYN

February 14–20, 1998—**Perinatal Medicine.** Westin Maui Hotel, Maui, HI. Mon.–Thur. 20 hrs. $625. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

February 12–15, 1998—**Office Gynecology and Women's Health for the Primary Care Physician.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Islandia San Diego. Method, AV, L, SB, W. $575. Thurs.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 28–March 3, 1998—**15th Annual OB/GYN Update: 1998.** UC Davis Medical Center at South Lake Tahoe. Sat.–Tues. Contact: (916) 734-5390.

OCCUPATIONAL & ENVIRONMENTAL

March 30– April 3, 1998—**Occupational & Environmental Medicine V.** UCSF at Radisson Miyako Hotel, San Francisco. Sun.–Thurs. 40 hrs. $750. Contact: UCSF (415) 476-5208.

May 15–16, 1998—**17th Annual Occupational & Environmental Medicine Symposium with Postgraduate Mini-Courses.** UC Davis at UCDMC Cancer Center Auditorium, Sacramento. Thurs.–Fri. Contact: UCD (916) 734-1394.

ONCOLOGY

December 7—**103rd Semi-Annual Seminar: Cutaneous Neoplasms.** California Tumor Tissue Registry at Sheraton Palace Hotel San Francisco. $265. Sun. 8 hrs. Contact: Loma Linda University (909) 824-4788.

January 16–17, 1998—**Radiotherapy to Reduce Restenosis.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri.–Sat. 16.5 hrs. Contact: Laurel Steigerwald, Scripps Clinic Dept. Academic Affairs 403c, 10666 N. Torrey Pines Road, La Jolla, 92037 (619) 554-8556.

January 29–31, 1998—**Hematology and Oncology: Current Concepts and Controversies.** UCSF at Radisson Miyako Hotel, San Francisco. Thurs.–Sat. $395. Contact: UCSF (415) 476-5208.

February 16–19, 1998—**Clinical Hematology & Oncology.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel La Jolla. Fri.–Mon. 24 hrs. Contact: Laurie A. Regis, Scripps Clinic (619) 554-8556.

OPHTHALMOLOGY

May 9, 1998—**Pearls of Ocular Therapy.** Scripps Clinic at Scripps Clinic, La Jolla. Sat. 7 hrs. Contact: Laurie A. Regis, Scripps Clinic (619) 554-8556.

May 29, 1998—**UC Davis Annual Ophthalmology Symposium.** UCD at Sacramento Hilton. Fri. 7 hrs. Contact: UCD (916) 734-1394.

ORTHOPEDICS

April 23–26, 1998—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency San Francisco. Method, AV, L, SB, W. $575. Thurs.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

May 3–6, 1998—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Las Vegas. Sponsored by Continuing Medical Education Associates. Caesar's Palace Las Vegas. Method, AV, L, SB, W. $575. Sun.–Wed. 20 hrs. credit: AMA, AOA, AAP, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

PEDIATRICS

December 6–7—**Stabilization and Management of Critically Ill Child.** UCSF at Embarcadero Hyatt Regency Hotel San Francisco. Sat.–Sun. Contact: UCSF (415) 475-4251.

January 24, 1998—**Update in Behavioral/Developmental Pediatrics.** UCSF at campus of UCSF. Sat. Contact: UCSF.

February 6–11, 1998—**PREP the Course.** AAP at Fairmont Hotel San Francisco. Fri.–Wed. 44 hrs. Contact: AAP (800) 433-9016, ext. 6796 or 7657.

February 15–18, 1998—**Pediatrics Update 1998.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Islandia San Diego. Method, AV, L, SB, W. $575. Sun.–Wed. 20 hrs. credit: AMA, AOA, AAP, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 16–19, 1998—**Clinical Hematology and Oncology: 1998.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel La Jolla. Fri.–Mon. 24 hrs. Contact: Laurie A. Regis, Scripps Clinic (619) 554-8556.

May 7–9, 1998—**31st Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs.–Sat. Contact: OCME (415) 476-4251.

PSYCHOLOGY

March 28, 1998—**Advanced Psychopharmacology for Clinicians: Practical Strategies for Management and Treatment of Refractory Schizophrenia, Bipolar Disorder and Depression.** UC Davis at Cancer Center Auditorium, Sacramento. Sat. 4hrs. $60. Contact: UCD (917) 734-5390.

RADIOLOGY

January 16–17, 1998—**Radiotherapy to Reduce Restenosis.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri.–Sat. 16.5 hrs. Contact: Laurel Steigerwald, Scripps Clinic Dept. Academic Affairs 403c, 10666 N. Torrey Pines Road, La Jolla, 92037 (619) 554-8556.

April 17–19, 1998—**4th Annual Breast Imaging and Interventions.** UCSD at San Diego Hilton. Fri–Sun. 20 hrs. $350. Contact: OCME (619) 534-3940.

SURGERY

December 12–13—**Annual Advanced Seminar in Urologic Surgery.** UCSF at Ritz-Carlton Hotel San Francisco. Fri.–Sat. 14.5 hrs. Contact: UCSF (415) 476-4251.

January 9–10, 1998—**What's New in General Surgery: 20th Annual Postgraduate Course.** UC Davis at Hyatt Regency Sacramento. Fri.–Sat. 12.75 hrs. $280. Contact: UCD (916) 734-5390.

April 16–18, 1998—**Recent Advances in Stem Cell Transplantation.** UCSD at San Diego Hilton. Thurs.–Sat. 20 hrs. $350. Contact: OCME (619) 534-3940.

April 16–18, 1998—**Techniques in Arthritis Surgery.** Ritz-Carlton Huntington Hotel, Pasadena. Wed.–Sat. 24 hrs. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

May 9, 1998—**Thyroid Update '98.** Sheraton Grande Hotel, Los Angeles. Sat. 7 hrs. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

UROLOGY

April 23–25, 1998—**International Bladder Research Congress.** UCSF at San Francisco. Thurs.–Sat. 17.5 hrs. $290–$395. Contact: (415) 476-5808.

GENERAL/MULTIDISCIPLINARY

December 5–6—**The Emerging Role of Hospitalists in American Health Care: A National Conference.** UCSF at Stanford Court Hotel,San Francisco. Fri.–Sat. 10 hrs. $350. Contact: UCSF (415) 476-5208.

December 5–8—**Spanish for the Medical Profession.** Los Angeles. Maricopa Health System. $695. 36 hrs. Contact: Joanna Rios. 1351 E. Ft. Lowell Road, Suite C, Tucson, AZ 85719. (619) 218-4875 or (520) 881-3295.

December 6–7—**Courtroom Communications: Qualifying and Testifying.** Medical Education Collaborative at Hyatt Newporter Hotel, Newport Beach. Sat.–Sun. 16.5 hrs. $375–$425. Contact: Dr. Benjamin (800) 355-9915.

January 28–31, 1998—**Medicine Meets Virtual Reality: Art, Science, Technology: Healthcare (R)Evolution.** San Diego Hyatt Regency. Wed.–Sat. Contact: AMA, Inc. (760) 741-8841.

January 31–February 2, 1998—**Spanish for the Medical Profession.** San Diego. Maricopa Health System. $695. 36 hrs. Contact: Joanna Rios, 1351 E. Ft. Lowell Road, Suite C, Tucson, AZ 85719. (619) 218-4875 or (520) 881-3295.

February 13–16, 1998—**California Academy of Family Physicians 50th Annual Scientific Assembly.** Anaheim Hilton and Towers. $275–$385. 26+ hrs. Contact: Clark W. Franklin, California Academy of Family Physicians, 114 Sansome St., Suite 1305, San Francisco, CA 94104-3824. (415) 394-9121; fax (415) 394-9119; Email: cfranklin@familydocs.org.

February 25–March 1, 1998—**7th Annual Winter Board Review for Physician Assistants.** Holiday Inn, Pasadena. Wed.–Sun. 30 hrs. $345; $245 student rate. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

HOME STUDY/SELF-ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA. PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list

CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

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U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

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Brochures, course information, and registration forms are available from the contact person or organization.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

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January 24–25, 1998—**16th Annual Albuquerque Family Practice Seminar.** Radisson Hotel Carlisle at I-40, Albuquerque. Sponsor: New Mexico Academy of Family Physicians. Contact: Ann Woodrow, (505) 243-4560..

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March 20–21, 1998—**Advances in Primary Care.** Albuquerque. Crowne Plaza Hotel. Contact: UNM Continuing Medical Education, Campus Box 713, Albuquerque, NM 87131-5126. (505) 272-3942, fax (505) 272-8604.

SATELLITE COURSES

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COURSE SPONSORS AND CONTACT INFORMATION

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U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

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WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

OTHER CME OPPORTUNITIES

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AMERICAN COLLEGE OF MEDICAL GENETICS. February 27–March1, 1998—**5th Annual Meeting & 29th Annual March of Dimes Clinical Genetics Conference**. Bethesda, Md. Up to 17.5 hrs. Contact: ACMG, 9650 Rockville Pike, Bethesda, MD 20814. (301) 530-7127; Fax (301) 571-1895; E-mail, mgross@genetics.faseb.org.

AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE. April 24–May 1, 1998—**57th American Occupational Health Conference**. Boston, Mass. Contact: ACOEM, 55 W. Seegers Rd., Arlington Heights, Ill 60005. (847) 228-6850, ext. 184, FAX (847) 228-1856; Website: www.acoem.org.

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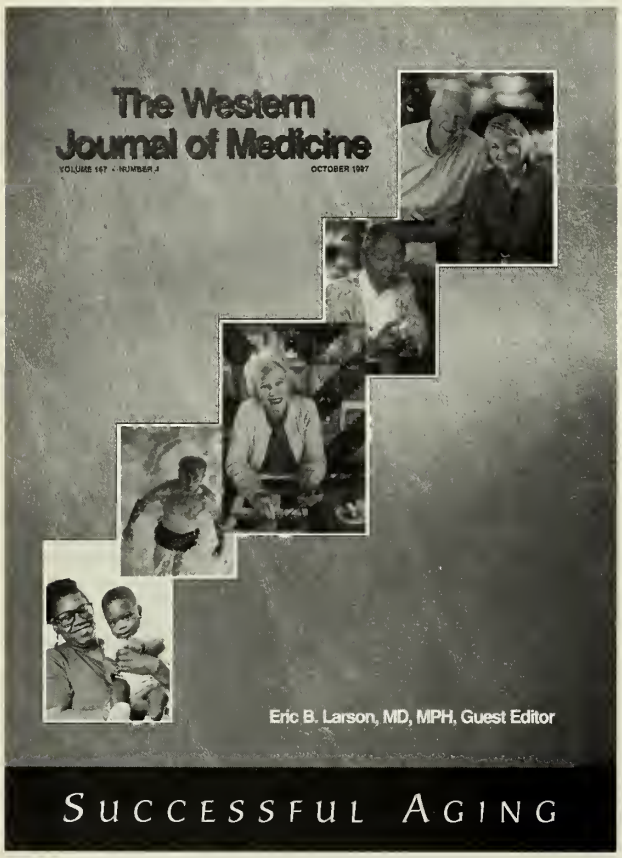

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Articles

AIDS-Related Disseminated Histoplasmosis in San Francisco, California

DAVID N. FREDRICKS, MD, *Stanford, California*; NOPPAMAS ROJANASTHIEN, MD, *Chiang Mai, Thailand*; *and* MARK A. JACOBSON, MD, *San Francisco, California*

The published reports of patients with the acquired immunodeficiency syndrome (AIDS) with disseminated histoplasmosis come mostly from institutions located in endemic areas for histoplasmosis, where disease is thought to occur by either primary infection or reactivation. The characteristics of reactivation disease are not well delineated. We describe the clinical features of reactivation disseminated histoplasmosis in 46 residents of San Francisco, California, with AIDS who did not report recent travel to an area endemic for histoplasmosis. Patients presented with illness lasting days to months, manifested most frequently by fever, chills, sweats, cough or dyspnea, gastrointestinal complaints, malaise, and weight loss. Physical examination and imaging studies were notable for hepatosplenomegaly, lymphadenopathy, or abnormal pulmonary findings in more than half of patients. Laboratory studies revealed a high rate of cytopenia, elevated serum lactate dehydrogenase levels, abnormal liver function test values, respiratory alkalosis with hypoxemia, and a median CD4 lymphocyte count of 36 × 10^9 per liter. The clinical presentation of reactivation disseminated histoplasmosis in patients with AIDS living in San Francisco is similar to that of disseminated histoplasmosis reported in patients with AIDS living in endemic areas. Reactivation disseminated histoplasmosis should be considered in any AIDS patient with a low CD4 lymphocyte count, a febrile illness, and a history of travel or residence in an endemic area.

(Fredricks DN, Rojanasthien N, Jacobson MA. AIDS-related disseminated histoplasmosis in San Francisco, California. West J Med 1997; 167:315–321)

The fungus *Histoplasma capsulatum* is endemic in the central United States and in areas of Latin America, the Caribbean, Africa, and Southeast Asia, with cases of disease reported from all continents.[1] The hyperendemic area in the United States includes the Mississippi and Ohio river valleys and extends south into Louisiana and the Gulf Coast. Patients with the acquired immunodeficiency syndrome (AIDS) with active *H capsulatum* infection tend to present with a severe illness marked by dissemination. Urban centers within the hyperendemic area such as Indianapolis, Indiana, and Kansas City, Missouri, have reported an incidence of histoplasmosis in patients with AIDS as high as 26%.[2] Several reports have described the clinical features of disseminated histoplasmosis in AIDS patients from endemic areas.[2–4] These cases may represent a mixture of two patient populations. The first group of patients are those in whom an acute pulmonary infection with *H capsulatum* develops that is not contained, leading to early dissemination. The second group consists of those in whom latent *H capsulatum* infection reactivates from a previous infection and subsequently disseminates, in a manner reminiscent of reactivated tuberculosis. The relative importance of each mechanism of dissemination has been debated but is not known.[5,6] Even a prospective study of histoplasmosis in patients infected with the human immunodeficiency virus (HIV) living in the endemic area of Kansas City was not able to determine the contribution of these two mechanisms, probably because of the high rate of skin test anergy and aberrant serologic responses in these patients.[32] It is also not clear whether reactivation histoplasmosis presents in the same manner as acute disseminated disease in patients with AIDS. By analyzing the clinical characteristics of a large group of AIDS patients diagnosed with disseminated histoplasmosis while liv-

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Supported by the San Francisco Center for AIDS Research, National Institutes of Health AI27763, and the University of California Universitywide AIDS Research Program, University of California, San Francisco, AIDS Clinical Research Center grant 95-R-CC86SF. Dr Rojanasthien was supported by a Merck Fellowship in Clinical Pharmacology.

Reprint requests to David N. Fredricks, MD, Division of Infectious Diseases S-156, Stanford University School of Medicine, Stanford, CA 94305.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus
HPA = *H capsulatum* polysaccharide antigen

ing in a nonendemic area (California) and without recent acute exposure, we sought to study reactivation disease in isolation.

Patients and Methods

Patients with disseminated histoplasmosis and AIDS were identified through a review of medical record discharge diagnoses and microbiology culture logs from San Francisco General Hospital Medical Center and Moffitt-Long Hospital in San Francisco, California, between 1981 and 1994. Disseminated histoplasmosis was defined by the presence of extrapulmonary *H capsulatum* detected by culture, peripheral blood smear, or histopathologic examination in association with an acute illness. Reactivation disease was defined as disease in a San Francisco resident who did not report travel within the previous three months to an endemic area. Because the incubation period for acute histoplasmosis may be as long as three weeks, a three-month period without exposure to the fungus was chosen to exclude patients who might have acute disease with subsequent dissemination. None of the patients in this study with documented disseminated histoplasmosis had symptoms for longer than three months. Criteria outlined by the Centers for Disease Control and Prevention were used to define AIDS.[7] All cases were studied retrospectively. Data were extracted from medical records using a case record form and entered into a database (Paradox) for analysis.

Results

Patient Characteristics

A total of 76 patients were initially identified as having histoplasmosis by discharge diagnosis or culture. Of these, 13 were excluded because they were HIV-negative and 7 because of incomplete or absent medical records. Two patients were excluded because the diagnosis of histoplasmosis could not be confirmed. Of the 54 remaining cases, 8 were excluded because they were not San Francisco residents or were documented to have traveled within three months of illness to an area endemic for histoplasmosis, leaving 46 patients with AIDS for the evaluation of disseminated histoplasmosis.

The median age of the 46 patients studied was 36 years (range, 21 to 60), and 45 patients were male (98%). The racial composition of the group consisted of 21 white non-Hispanic (46%), 18 Hispanic (39%), 4 African-American (9%), and 3 Asian (6%) patients. Previous opportunistic infections or malignant neoplasms were noted in 42 patients (91%). Active opportunistic coinfections were present at the time of diagnosis in 25 patients (54%) (Table 1).

Table 1.—*Active Coinfections Present at Diagnosis of Disseminated Histoplasmosis*

Infection	*Patients Infected (n = 46), No. (%)*
Cytomegalovirus	9 (20)
Mycobacterium avium	8 (17)
Pneumocystis carinii pneumonia	7 (15)
Intestinal parasites	7 (15)
Bacteremia	5 (11)
Herpes simplex virus	5 (11)
Kaposi's sarcoma	4 (9)
Candidiasis	2 (4)

A documented travel history to an area endemic for histoplasmosis was obtained in 40 of 46 patients (87%). Of the 40 cases with known exposure, 34 patients were born in an endemic area (85%) and 6 patients were born outside of but traveled through endemic areas (15%). Of the 40 patients, 21 (53%) were exposed in the United States, 15 (38%) in Latin America or the Caribbean, 3 (8%) in both areas, and 1 (3%) in Asia. The time interval since last known travel to an endemic area was documented in 23 cases. The median time to last exposure was two years (range, 0.25 to 23 years).

Clinical Presentation

Patients' chief complaints, by order of frequency, were fever, cough, shortness of breath, abdominal pain, skin or oral lesions, and diarrhea. Duration of the chief complaint varied between 2 and 90 days, with a median of 14 days. In the 46 patients studied, 43 had fever (93%), 33 noted chills or sweats (72%), 27 reported weakness or malaise (59%), and 22 had weight loss (48%). These symptoms tended to be subacute, lasting for weeks before diagnosis in most patients. Table 2 lists symptoms by the most frequently involved organ systems, as well as physical findings. Results are compared with studies of AIDS patients from the endemic areas of Indianapolis, Indiana, and Houston, Texas.[2,3]

Physical findings were notable for fever, with 39 (85%) patients having a temperature higher than 38.5°C (101.3°F) before treatment. The median maximum temperature recorded during the evaluation of illness in the days to weeks before treatment was 39.8°C (103.6°F), with a range of 36.9°C to 41.0°C (98.4°F to 105.8°F). Thirteen patients had a systolic blood pressure of less than 90 mm of mercury (28%). The median pulse was 100 beats per minute with a range of 72 to 140. The median respiratory rate was 20 breaths per minute with a range of 16 to 40. Organomegaly was listed if enlargement was noted on physical examination or radiographic or ultrasonographic imaging.

The results of laboratory tests are summarized in Table 3. Only 1 patient of the 46 had a hemogram at

Table 2.—*Symptoms and Physical Findings in the Study Patients Compared With Reports of Similar AIDS Patients From Endemic Areas*

	Present Study, n = 46 No. (%)	*Wheot et al., 1990[2], n = 72* No. (%)	*Johnson et al., 1988[3], n = 48* No. (%)
Symptoms by organ system			
Constitutional (fever)	43 (93)	69 (96)	39 (81)
Respiratory	31 (67)	38 (53)	10 (21)*
Gastrointestinal	30 (65)	2 (3)	9 (19)†
Nervous system	15 (33)	13 (18)	—
Integument	14 (35)	1 (1)	—
Physical findings			
Hepatomegaly	22 (48)	19 (26)	9 (19)
Splenomegaly	28 (61)	9 (12.5)	15 (31)
Lymphadenopathy	26 (57)	12 (17)	9 (19)
Skin lesions	14 (30)	1 (1)	>5 (>10)
Mucosal ulceration	10 (22)	—	—
Abnormal pulmonary	28 (61)	—	—
Abnormal CNS	7 (15)	—	—
Abdominal tenderness	16 (35)	—	—

CNS = central nervous system.
*Cough.
†Diarrhea.

diagnosis that was normal in all three cell lines. Pancytopenia was present in 21 patients (46%). At least one liver function test abnormality was present in 38 patients at diagnosis (83%). Eight patients had ferritin levels greater than 1,000 µg per liter (>1,000 ng per ml), and one patient had a level of 21,240 µg per liter (21,243 ng per ml). Arterial blood gas measurements revealed respiratory alkalosis in 24 of 28 patients tested (86%). Chest radiograph findings are described in Table 4.

Microbiology results are shown in Table 5. A total of 41 patients had blood specimens drawn for culture before therapy, with most patients getting multiple blood cultures, producing 132 specimens, of which 95 specimens eventually grew *H capsulatum*. Out of the 41 patients, 36 had at least one positive blood culture (88%). The median time between drawing a specimen for culture and its turning positive was 17 days, with a range of 6 to 52 days.

Pathology specimens were positive on histologic examination in 34 of 43 specimens, for a rate of 79% overall. Bone marrow biopsy was positive in 11 of 15 cases (73%), lymph node biopsy in 8 of 9 cases (89%),

Table 3.—*Laboratory Data for Study Patients at the Time of Diagnosis*

Test	*Normal Range*	*Median*	*Range*	*Patients With Abnormal Values, No.*	*Patients Tested, No.*
Hematocrit	39.8–52.2	29.8	17.5–45.0	43	46
Leukocyte count, × 10^9/liter	3.9–11.7	2.65	0.6–9.4	33	46
PMN, × 10^9/liter	1.7–8.0	1.9	0.5–7.7	18	43
Left shift	Absent			38	44
Platelets, × 10^9/liter	150–400	109	25–443	29	46
CD4 cells, × 10^9/liter	420–1,250	36	2–150	35	35
Bilirubin, mg/dl	0.1–1.2	0.55	0.1–5.5	6	46
AST, IU/liter	10–50	83	7–1,113	36	46
Alk Phos, IU/liter	30–115	183	43–1,730	34	45
LDH, IU/liter	110–220	509	164–5,760	35	38
PT, sec	<13.1	12.6	9.8–19.9	16	41
Creatinine, mg/dl	0.6–1.4	0.95	0.4–7.0	5	44
Arterial blood gases pH	7.35–7.45	7.45	7.15–7.64	12	28
Po_2, mmHg	80–100	72	32–100	22	28
Pco_2, mmHg	35–45	30	20–39	24	28

Alk Phos = alkaline phosphatase, AST = aspartate aminotransferase, LDH = lactate dehygrogenase, PMN = polymorphonuclear leukocytes, PT = prothrombin time.

Table 4.—*Chest Radiograph Findings in This Study Compared With 2 Studies From Areas Endemic for Histoplasmosis*

Finding	Present Study, n = 46 No. (%)	Wheat et al., 1990[2], n = 72 No. (%)	Sarasi and Johnsan, 1992[4], n = 59 No. (%)
Normal	9 (20)	31 (43)	16 (27)
Abnormal	37 (80)	41 (57)	43 (73)
Diffuse infiltrate	27 (59)	32 (44)	34 (58)
Focal infiltrate	6 (13)	8 (11)	5 (8)
Lymphadenopathy	15 (33)	2 (3)	—
Calcified granuloma	7 (15)	2 (3)	2 (3)

skin biopsy in 5 of 5 cases (100%), bronchoalveolar lavage in 4 of 7 cases (57%), transbronchial biopsy in 2 of 2 cases, liver biopsy in 1 of 2 cases, and esophageal biopsy in 1 case. Hemoperitoneum developed in one patient who underwent liver biopsy, and the patient died. The median time from biopsy to pathology report was 2 days with a range of 1 to 15 days. A peripheral blood smear for intracytoplasmic yeast was positive in 9 of 13 cases (69%), with a turnaround time of 1 day or less.

Diagnosis

The initial or admitting diagnosis before microbiologic or pathologic confirmation was recorded for each patient. Common diagnoses were fever, pneumonia, pancytopenia, lymphadenopathy, and rule out *Pneumocystis carinii* pneumonia, Mycobacterium avium-complex bacteremia, tuberculosis, fungal infection, or lymphoma. Only 6 patients had fungal infection listed in the differential diagnosis, and just 1 of the 46 patients in this study had disseminated histoplasmosis specifically listed in the differential diagnosis of the presenting illness.

The diagnosis of disseminated histoplasmosis was not made in 4 patients, 2 of whom died before diagnosis and 2 of whom were lost to follow-up. In the 42 remaining patients, the method of first successful diagnosis was determined by establishing which diagnostic route led to identification of the disease and the initiation of treatment. Histoplasmosis was first diagnosed by histopathologic examination in 25 patients (60%), with the most frequent sites being bone marrow (7 patients), lymph node (6 patients), bronchoscopic biopsy or lavage (5 patients), and skin (3 patients). Culture for *H capsulatum* first revealed the diagnosis in 11 patients (26%), with blood the most frequent source, leading to a diagnosis in 9 patients. Review of the peripheral blood smear for intracytoplasmic yeast in leukocytes first revealed the diagnosis in 6 patients (14%).

Discussion

This retrospective case series of 46 patients represents the largest group of patients with AIDS and disseminated histoplasmosis from a nonendemic area reported to date,[8,9] although individual case reports have also described reactivation disseminated histoplasmosis in both patients with AIDS and those without AIDS.[10–13] Although histoplasmosis has been noted to occur in as many as 26% of AIDS patients from endemic areas, it has been suggested that the disease develops in less than 1% of AIDS patients from nonendemic areas.[5] The relatively low incidence of this opportunistic infection in AIDS patients residing in nonendemic areas may hamper its diagnosis, especially when other concurrent opportunistic infections are present (as occurred in half the cases we reviewed) that could explain clinical and laboratory abnormalities. In this study, physicians specifically listed histoplasmosis in their initial differential diagnosis of the presenting ill-

Table 5.—*Microbiology Results for* H capsulatum *Listed By Site Cultured*

Site Cultured	Present Study: Patients With Positive Culture, No.	Present Study: Total Patients, No. (%)	Wheat et al., 1990[2]: Patients With Positive Culture, No.	Wheat et al., 1990[2]: Total Patients, No. (%)
Blood	36	41 (88)	32	35 (91)
Bone marrow	13	14 (93)	19	21 (90.5)
Respiratory	12	14 (86)	18	21 (86)
Lymph node	6	7 (86)	6	7 (86)
Urine	0	3 (0)	2	6 (33)
Cerebrospinal fluid	0	13 (0)	2	10 (20)
Liver	1	1 (—)	1	1 (—)
Skin	3	5 (60)	—	—

ness in only one patient. Greater awareness of this disease is needed in nonendemic areas such as the western United States.

Disseminated histoplasmosis is thought to occur by either primary infection, through the inhalation of exogenous fungal spores, or the reactivation of latent infection with previously acquired endogenous organisms. In nonendemic areas such as San Francisco, the lack of exogenous *H capsulatum* in the environment implicates the reactivation of latent infection as the source of disseminating organisms. Although histoplasmosis outbreaks have been documented in areas considered to be nonendemic such as Maryland[14] and central New York State,[15] these locations are relatively close to the endemic area, and *H capsulatum* was cultured from the outbreak sites, suggesting that microfoci of *H capsulatum* were responsible for the outbreaks.

In contrast, California is geographically isolated from the endemic area, and there are no published reports of histoplasmosis outbreaks or the detection of environmental *H capsulatum* from California using a Medline search from 1966 through 1996. The published cases of histoplasmosis from California have occurred in patients who have lived or traveled in endemic areas.[16,17] Although studies of histoplasmin skin test reactivity among large populations such as navy recruits demonstrate that positive histoplasmin skin tests can be found in people residing in California,[18] the data are most consistent with these tests representing cross-reactivity to *Coccidioides immitis*.[16,19,20] Because no microfocus of *H capsulatum* has been reported in California or the western United States, acute exposure with dissemination is highly unlikely.

Molecular evidence of reactivation disease in AIDS-associated disseminated histoplasmosis was presented by Keath and co-workers using restriction fragment length polymorphisms of *H capsulatum* nuclear and mitochondrial genes.[21] We think that this population of patients with AIDS living in California represents a relatively uniform collection of patients with reactivation histoplasmosis. Half of the patients were documented to have only a remote exposure to *H capsulatum*, and those patients known to have recently traveled to an endemic area were excluded from the study. All of the patients were residents of the San Francisco area. One patient had lived exclusively in San Francisco for 23 years after emigrating from El Salvador in Central America. There were no significant differences in clinical variables between the 23 patients with a chronologic travel history and the 23 patients without (data not shown). In their review of disseminated histoplasmosis in AIDS patients, Wheat and colleagues state, "Contrasted to tuberculosis, in which reactivation appears to be the common mechanism of infection in adults, reactivation appears to be infrequent in histoplasmosis."[2(p368)] Although this statement may be true in endemic areas, in nonendemic areas such as San Francisco, reactivation histoplasmosis is the only tenable explanation for most of the cases of disseminated histoplasmosis in AIDS.

A review of the clinical presentations in these 46 patients highlights the difficulty in making a diagnosis of disseminated histoplasmosis. Patients tended to present with nonspecific symptoms such as fever, chills, sweats, weakness, cough, or weight loss. These symptoms are compatible with many common afflictions in AIDS, including *M avium*-complex bacteremia, *P carinii* pneumonia, lymphoma, tuberculosis, and bacterial pneumonia. Symptoms were present for days to months before diagnosis. Physical examination findings or imaging studies frequently revealed hepatomegaly (48%), splenomegaly (61%), and lymphadenopathy (57%), consistent with the known predilection of *H capsulatum* for the reticuloendothelial system. These figures are similar to data derived from a study of abdominal computed tomographic findings in AIDS patients with disseminated histoplasmosis.[22]

Multiple laboratory abnormalities are usually present in AIDS patients with disseminated histoplasmosis, and these can provide a clue to the diagnosis. Only 1 patient of the 46 had a normal hemogram at diagnosis. We cannot exclude the possibility that the concurrent use of medications (such as zidovudine) may have contributed to these hematologic abnormalities, but the presence of cytopenia in patients receiving no medications argues that histoplasmosis alone may produce these effects. A leftward shift was noted on the examination of leukocytes in 86% of patients, although no patient had an elevated absolute leukocyte count. Although ferritin levels were measured in only a few patients in this study before treatment, we observed striking hyperferritinemia in several patients. Hyperferritinemia has been described before in AIDS-associated disseminated histoplasmosis, with one report of a patient with a ferritin level of 426,000 μg per liter.[23] Our experience with patients having disseminated histoplasmosis suggests that elevated ferritin levels rapidly fall with treatment and rise again with relapse.[24] Abnormal liver function test results were common, with at least one liver function test abnormality present in 83% of patients. Although lactate dehydrogenase levels were elevated in 92% of patients, the tissue source of this elevated enzyme is not known in these patients.

Pulmonary involvement in this disease is reflected in the high rate of abnormal chest radiographs and arterial blood gas analyses. Pulmonary involvement clearly does not distinguish between primary and reactivation histoplasmosis.

Microbiologic evaluation of these patients was usually successful but was not expedient. Although blood cultures were positive in 88% of patients, there was a substantial delay between drawing the specimen and obtaining a result. The median time to a positive blood culture was 17 days. One patient's blood culture did not turn positive until after 52 days of incubation. This delay explains why most patients were diagnosed by histopathologic examination despite having a high rate of positive cultures. A routine liquid media culture system was used in this study, which may require longer

incubation times and produce lower yields than obtained with a lysis-centrifugation system.[25,26] Another problem with standard blood cultures is that the specimens are routinely discarded after only five to seven days of incubation, which is insufficient time to grow *H capsulatum*. A high index of suspicion for histoplasmosis should lead health care professionals to obtain several blood specimens for culture, preferably lysis-centrifugation culture, with specific instructions for the laboratory to hold the culture for at least four weeks.

Histopathologic examination was also successfully used to make the diagnosis of histoplasmosis in a high percentage of patients, with 79% of specimens submitted being positive, but the time from test to result was much shorter than with culture. A median of two days elapsed between biopsy and pathology report, compared with 17 days for culture. The disadvantage of histopathology is the need for invasive procedures, but the advantage is the speed of diagnosis, which is paramount in acutely ill patients. Examination of the peripheral blood smear or buffy-coat preparation for identifying intracytoplasmic yeast in leukocytes is a cheap, rapid, noninvasive test with a yield of 69% in the 13 patients tested here and with a turnaround time of only one day. The disadvantage of the blood smear examination is that some experience is necessary for the correct identification of the yeast within leukocytes, and sensitivity of this test may be suboptimal.

Although no patient in this study had the initial diagnosis made by the *H capsulatum* polysaccharide antigen (HPA) test, HPA testing of blood and urine appears to be useful in diagnosing disseminated histoplasmosis in AIDS patients.[27,28] As for serologic tests, investigators have questioned the usefulness of serologic tests in AIDS patients with disseminated histoplasmosis.[5,29] There is no role for histoplasmin skin testing in the diagnosis of disseminated histoplasmosis.[30,31]

We suggest a diagnostic strategy for the evaluation of AIDS patients with suspected disseminated histoplasmosis based on both the yield and speed of each test. Early evaluation should include phlebotomy for blood cell counts and serum chemistry values (lactate dehydrogenase, ferritin, liver function tests), a peripheral blood smear for the detection of yeasts, and blood cultures (lysis-centrifugation). Abnormal laboratory test results help to drive further diagnostic evaluation, including invasive tests. The peripheral blood smear provides the opportunity for the immediate diagnosis and initiation of treatment, whereas the blood culture may provide a delayed diagnosis or may help confirm the diagnosis suggested by other means. Specimens for culture should be sent to the laboratory with specific instructions to incubate them for four to six weeks. In ill patients who require immediate intervention, further evaluation should include either tissue biopsy with histopathologic examination and culture or HPA testing of serum and urine. Bone marrow is a tissue that is relatively easy and safe to obtain, and it provides a good yield on both histologic examination and culture.

Although comparisons between this study of AIDS patients living in a nonendemic area and of those living in endemic areas are subject to numerous biases, some general conclusions are warranted. The clinical presentations of AIDS patients with disseminated histoplasmosis appear to be similar in both endemic and nonendemic areas. A notable exception was the higher incidence of lymphadenopathy noted on chest radiographs from patients in San Francisco (33%) compared with those in Indianapolis (3%).[2] This discrepancy may be due to institutional differences in radiologic interpretation, but the tenfold difference seems rather large for this alone.

In summary, disseminated histoplasmosis may occur as reactivation disease in patients with AIDS and should be considered in any AIDS patient with a low CD4 lymphocyte count, a febrile illness, and a history of travel or residence in an endemic area, even when other concurrent opportunistic infections are present. The clinical features of reactivation disseminated histoplasmosis in AIDS are similar to those found in AIDS patients residing in endemic areas. Multiple laboratory test abnormalities may help suggest the diagnosis. In patients who are critically ill with suspected disseminated histoplasmosis, rapid diagnosis by tissue biopsy or HPA testing of urine and serum should be undertaken, and early (empiric) initiation of antifungal therapy may be warranted.

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Articles

Intramuscular High-Dose Triamcinolone Acetonide in the Treatment of Severe Chronic Asthma

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We describe our experience with administering intramuscular triamcinolone acetonide to 22 steroid-dependent patients with asthma. These patients represent the minority of those with asthma whose disease is characterized by frequent emergency department visits, hospital admissions, and long-term dependency on oral corticosteroid therapy. The participants were randomly assigned to 2 treatment groups, one group receiving 120 mg of intramuscular triamcinolone acetonide, the second receiving 360 mg as a series of three 120-mg daily doses. We determined relative efficacy by comparing peak expiratory flow rates and incidents of emergency department visits, hospital admissions, and ventilatory failure of the study and during the 12 months before enrollment. Peak expiratory flow rates improved significantly in both groups. The mean (± standard deviation [SD]) monthly percentage of predicted peak expiratory flow on the study was 88.6 ± 3.7% and 91.2 ± 3.9% compared with 63 ± 15.1% and 64 ± 14.5% at entry in patients receiving 120 and 360 mg, respectively ($P < 0.02$). Patients receiving 120 mg required 8 hospital stays and 8 emergency department visits compared with 27 hospital stays and 72 emergency department visits in the previous year ($P < 0.05$). Patients receiving 360 mg required 5 hospital stays and 5 emergency department visits compared with 33 hospital stays and 34 emergency department visits in the previous year ($P < 0.05$). The average monthly interval (± SD) between exacerbations was 2.7 ± 2.3 and 7.8 ± 3.5 for patients receiving 120 mg and 360 mg, respectively. A total of 25 intubations was required in the previous year and only 1 during the study. The incidence of cushingoid facies, weight gain, and hypertension was reduced in both groups ($P < 0.05$). Total steroid use was reduced in both groups ($P < 0.02$). A dose of 360 mg produced a longer exacerbation-free period than 120 mg ($P < 0.02$).

(Mancinelli L, Navarro L, Sharma OP. Intramuscular high-dose triamcinolone acetonide in the treatment of severe chronic asthma. West J Med 1997; 157:322–329)

Corticosteroids have been used both in the treatment of asthma and as maintenance therapy for the past 40 years. Parenteral steroids are usually used when patients are admitted to the hospital for acute exacerbations of asthma. Clinicians typically convert parenteral steroids to oral steroids when clinical symptoms and pulmonary function improve. Patients are frequently discharged with a regimen of oral steroids on a tapering schedule, supplemented by an inhaled steroid preparation using metered-dose inhalers. Most patients with asthma have relatively mild disease that is controlled by inhaled agents—β_2-agonists, cromolyn sodium, and corticosteroids, frequently in combination. A small group of patients, however, have a more severe disease characterized by long-term dependency on oral steroid use, frequent emergency department (ED) visits, recurrent hospital admissions, and often the need for mechanical ventilation.

See Editorial, pages 359 and 360

Therapeutic agents such as gold,[1,2] methotrexate,[3,4] and troleandomycin,[5,6] as well as moderate doses of intramuscular triamcinolone acetonide,[7–9] have been used with varying success in patients with severe chronic asthma. More recently, a high-dose regimen of intramuscular triamcinolone acetonide demonstrated greater success in controlling symptoms in such patients than oral prednisone, but a number of steroid-associated side effects were worsened in the patients receiving triamci-

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ABBREVIATIONS USED IN TEXT

ED = emergency department
PEFR = peak expiratory flow rate
SD = standard deviation
SEM = standard error of the mean

nolone.[10,11] The increase in some steroid-associated side effects is consistent with that occurring in previous studies involving moderate doses of intramuscular triamcinolone acetonide.[7–9]

In this article we describe the experience with intramuscularly given triamcinolone acetonide in 22 steroid-dependent patients with chronic severe asthma. We set out to compare the efficacy and adverse effects associated with the use of two doses: 360 mg, the dose used earlier by others,[10,11] and a lower dose of 120 mg to minimize possible side effects. We find, as did other investigators,[11] that intramuscular triamcinolone acetonide is superior in efficacy to oral prednisone. Unlike in previous studies, however, the patients in our study were treated and maintained throughout with intramuscular triamcinolone as the sole parenteral corticosteroid. Supplemental oral corticosteroids were not used for maintenance, nor were they prescribed for or subsequent to acute exacerbations. We observed that the steroid-associated side effects noted at entry either decreased in incidence or remained unchanged during the course of the study. Our observations differ from the reports of previous investigators who noted an increase in steroid-associated side effects in their patients following treatment with intramuscular triamcinolone.[7–11]

Patients and Methods

We enrolled 22 steroid-dependent patients with asthma attending the Chest Clinic, Los Angeles County–University of Southern California Medical Center, Los Angeles, California. All patients fulfilled the criteria of the American Thoracic Society for the clinical diagnosis of asthma.[12] Patients were considered to be steroid dependent if they were currently taking oral steroids or had required more than one course of oral steroid therapy in the six months before admission. Patients with concurrent underlying disease, such as congestive heart failure, pneumonia, occupational or interstitial lung disease, severe hypertension, brittle diabetes, menorrhagia, immune suppression, or chronic obstructive pulmonary disease as defined by the American Thoracic Society criteria,[12] and those not able to comply with all study requirements, were excluded. None of the patients were smokers.

The patients were known to have poorly controlled asthma often over many years, during which time they had been maintained on oral prednisone therapy in an average daily dose of 14.4 mg (±5.4 mg) for a mean period of nine years (±6.4), in addition to aerosolized β_2-agonists and aerosolized corticosteroids. We considered these patients to be steroid dependent because between exacerbations all patients had required daily treatment with oral prednisone for at least a year. Any attempt to decrease or discontinue their daily oral steroid dose had resulted in worsening symptoms of asthma. Despite good compliance with maintenance oral prednisone therapy, these patients had often required courses of high-dose corticosteroids and hospital admissions because of worsening asthma. We considered our patients to have life-threatening asthma because in the year before our study, 15 patients had required admission to a hospital for asthma, and 10 of the 22 patients had required mechanical ventilation on at least one occasion. Eleven patients had evidence of cushingoid facies, four had borderline hypertension, three suffered from diabetes mellitus controlled with diet and oral medications, six were obese, and nine had gained weight during the previous year. No patients were withdrawn from the study after entry.

All patients were taking β_2-agonists by metered-dose inhaler (albuterol [Proventil], 2 puffs or 180 μg 4 times a day) and inhaled corticosteroids (triamcinolone acetonide, 2 puffs or 200 μg 4 times a day, or beclomethasone dipropionate, 2 puffs or 84 μg 4 times a day) when enrolled in the study. These medications were continued without change in dose or frequency during the study. Four patients were also taking an oral β_2-agonist (albuterol sulfate [Proventil SR]), and two patients were taking oral theophylline at entry into the study. These medications were also continued without change in dose or frequency throughout the study. All participants gave written informed consent after reading a detailed written explanation of the project. Approval was obtained from the Los Angeles County–University of Southern California Medical Center Institutional Review Board for Human Research.

The study was conducted as an unblinded self-controlled trial in which patients were randomly assigned by coin toss into one of two treatment groups that were defined by the dose of intramuscular triamcinolone acetonide given. One group received 120 mg, and the second group received a total of 360 mg over three consecutive days in 120-mg doses per day. The study provided for a complete record of a patient's medical history to be made at the time of the initial physical examination and for the patients' asthma to be clinically assessed. Patients were interviewed regarding the history of their asthma, smoking, allergies, occupation, asthma medications, and the number of hospital admissions, intubations, and ED visits during the 12 months before entry into the study. The information obtained was correlated with medical records from our institution and any additional institutions where the patients had received care. A standardized questionnaire format was used to determine the severity of symptoms of coughing, wheezing, shortness of breath, and chest tightness on a scale of 1 (least) to 5 (most). Physical findings, including vital signs and the results of chest examination for the presence of wheezing, were recorded. Theophylline levels in patients receiving theophylline, baseline 9 a.m. serum

cortisol levels, and spirometry results were also obtained. Patients were asked to chart their peak flow readings three times a day with a peak flow meter supplied to them.

Follow-up was accomplished by clinic visits. During each follow-up visit, initially at monthly intervals, patients were interviewed regarding symptoms of coughing, wheezing, shortness of breath, and chest tightness. They were also questioned about drug compliance, any hospital admissions or ED visits, and any side effects that they believed stemmed from their medications. Patients were asked specifically about the occurrence of gastrointestinal symptoms, skin rashes, bruising, and menstrual irregularities. A physical examination was performed and a blood count and routine blood chemistry values obtained. A peak flow reading recorded as the best of three attempted efforts was obtained. Asthma medications in place at the time of entry into the study were retained without adjusting dose or frequency, with the exception of maintenance oral prednisone therapy, which was discontinued in all patients after the initial treatment with intramuscular triamcinolone.

Wheezing and breathlessness abated after the first treatment with triamcinolone, but recurred after an interval. Patients presenting with exacerbations of asthma refractory to treatment with nebulized β_2-agonists were readministered intramuscular triamcinolone appropriate for their treatment group, and a therapeutic interval was established. Subsequent clinic appointments for follow-up were made for this interval of time. Patients were instructed to contact our study clinical nurse at any time for an immediate appointment should they have an exacerbation of their asthma. The study clinical nurse worked closely with the ED staff to review and document all ED visits by study patients. Any study patient judged to be having an exacerbation of asthma refractory to nebulized β_2-agonists was readministered intramuscular triamcinolone appropriate to their treatment group, observed and discharged, or admitted on the discretion of the ED staff.

Data were analyzed as part of a two-treatment, open-label study in which differences between treatment groups and before- and after-treatment effects were examined. Differences between groups at baseline were assessed with the Wilcoxon rank sum (Mann-Whitney U) test for continuous data and Fisher's exact test for dichotomous data. Changes from baseline were assessed with the Wilcoxon signed rank test for nonparametric data. Spirometry data for peak expiratory flow rates (PEFRs) were analyzed as the mean percentage of predicted value to minimize any effect caused by differences between groups in patient age, sex, race, or height. Differences between the two treatment groups with regard to monthly average peak flow values were assessed with the Wilcoxon rank sum (Mann-Whitney U) test. Fisher's exact test was used to analyze differences in the incidence of side effects observed during triamcinolone treatment compared with baseline. Exact binomial confidence intervals of 95% were provided for the true proportions of patients with adverse drug reactions. Correlations between measured plasma cortisol levels, triamcinolone dose group, and extent of oral steroid use before the study were analyzed by calculating the Spearman rank correlation coefficient. All tests were two-tailed, and an α value of 0.05 was used to indicate statistical significance.

Results

Characteristics of the patients at entry are shown in Table 1. There were no significant differences between treatment groups with regard to the duration of asthma, the number of hospital admissions, average maintenance doses of oral prednisone, or history of requiring mechanical ventilation during the year before the study.

Patients were monitored during the 12-month study period and were compared in terms of the duration of exacerbation-free intervals, the number of ED visits and hospital admissions, the necessity for mechanical ventilation, average monthly peak flow measurements, and the incidence of steroid-associated side effects.

Table 2 shows the mean (± standard deviation [SD]) percentage of PEFR as an average of the mean monthly figures for each treatment group. Analysis showed that intramuscular triamcinolone treatment resulted in a statistically significant improvement over baseline pretreatment values in both groups.

When average PEFRs for the two groups are compared for each month following treatment with triamcinolone, a significant difference is apparent after one month. Figure 1 shows the average PEFRs (liters per minute) by month in the two treatment groups during the study. Patients who received 360 mg of triamcinolone had higher average peak flow rates during each of the first seven months of follow-up than patients who received 120 mg of triamcinolone ($P = 0.01$). For PEFRs, differences between the two groups diminished to nonsignificance in the final months of follow-up (data not shown).

We compared the cumulative incidence of ED visits, hospital admissions, and intubations in each group during the study and in the year before the study (Figure 2A and B). Patients assigned to receive 120 mg of triamcinolone were admitted to the hospital a total of 8 times during posttreatment follow-up compared with 27 times in the previous year ($P < 0.05$). Their ED visits and instances of mechanical ventilation numbered 8 and 0 times, respectively, during the 12-month study period, as compared with 72 and 14 times, respectively, in the previous year ($P < 0.05$). Patients assigned to receive 360 mg of triamcinolone required 5 hospital admissions, 5 ED visits, and 1 instance of mechanical ventilation during the 12-month study period compared with 33 hospital admissions, 34 ED visits, and 5 intubations in the previous year ($P < 0.05$).

Throughout the study period, no significant difference was found between the two groups with respect to

TABLE 1.—*Characteristics of the Study Patients*

Patients	Age, yr/Sex	Baseline PEFR, % of Predicted	Asthma Duration, yr	Oral Prednisone, mg/day (Duration, yr) Before Study	Triamcinolone Treatment Group, mg/treatment	Intubations, No.	Hospital Admissions, No. in Previous Year	Emergency Department Visits, No.
1	48/F	280 (62)	46	12 (15)	360	0	0	0
2	52/F	140 (42)	50	15 (20)	360	5	5	0
3	61//F	140 (41)	50	10 (8)	360	1	1	1
4	45/F	250 (43)	35	5 (8)	360	0	2	0
5	40/F	360 (72)	40	20 (8)	360	0	0	0
6	59/M	300 (55)	9	10 (6)	360	0	0	0
7	73/F	120 (35)	12	20 (6)	120	1	12	12
8	34/F	300 (67)	4	20 (4)	120	6	1	12
9	37/F	280 (77)	8	10 (2)	360	2	2	2
10	49/F	250 (66)	40	10 (15)	120	0	0	3
11	42/F	240 (53)	32	20 (6)	360	2	2	0
12	59/F	230 (67)	16	10 (11)	120	0	3	6
13	57/F	230 (61)	30	20 (20)	120	1	5	9
14	47/F	140 (40)	18	10 (19)	120	4	4	2
15	39/M	390 (73)	8	20 (7)	120	0	0	2
16	70/F	160 (49)	15	5 (1)	360	0	2	2
17	61/F	240 (68)	34	20 (20)	360	0	11	20
18	44/M	200 (38)	30	15 (4)	360	1	2	2
19	43/F	260 (57)	7	20 (6)	120	0	0	11
20	58/F	240 (46)	34	20 (10)	360	0	6	7
21	56/F	200 (57)	20	10 (2)	120	2	3	3
22	30/F	260 (70)	3	20 (1)	120	0	0	12

PEFR = peak expiratory flow rate.

hospital admissions, ED visits, or requirements for mechanical ventilation. Figure 2-C shows the cumulative incidence of hospital admissions, ED visits, and intubations during the study in the two treatment groups ($P > 0.05$).

The two groups differed significantly, however, with respect to the length of time that elapsed before additional intramuscular triamcinolone was necessary to control symptoms of asthma. Figure 3 shows the average length of time for each patient between exacerbations of asthma requiring additional triamcinolone. The average interval (months ± SD) was 2.7 ± 2.3 months in the group that received 120 mg and 7.8 ± 3.5 months in the group that received 360 mg of intramuscular triamcinolone ($P < 0.02$).

A statistically significant improvement in adrenal function, as measured by serum cortisol levels, was observed during the study. Five patients who presented with abnormally low serum cortisol levels at entry had cortisol levels greater than 280 nmol per liter (>10 µg per dl) after six months ($P < 0.05$; data not shown). Three of these patients were treated with 120 mg, and two were treated with 360 mg of triamcinolone acetonide. Four of these five patients had a maintenance oral prednisone requirement of 5 to 10 mg daily before the study. The fifth patient had a daily oral prednisone requirement of 10 to 20 mg before the study. Adrenal function was considered to be normal if basal cortisol levels were higher than 280 nmol per liter, and cortisol levels after corticotropin stimulation rose by at least 190 nmol per liter (7 µg per dl) to a level higher than 550 nmol per liter (>20 µg per dl).

Only 3 of 22 patients had normal serum cortisol levels at the time of enrollment in the study. Two of these patients, who were treated with 360 mg of triamcinolone, retained normal serum cortisol values throughout the study. The third patient, who received 120 mg of triamcinolone, had an abnormally low serum cortisol level at six months.

During treatment with triamcinolone, total steroid doses required in each patient were significantly less

TABLE 2.—*Average Monthly Percentage of Predicted Peak Expiratory Flow Rate (PEFR)**

PEFR	Percentage	
	120-mg Group	360-mg Group
Baseline	63 ± 15	64 ± 14.5
After treatment	88.6 ± 3.7	91 ± 3.9
P†	< 0.02	< 0.02

*Values given as the mean ± standard deviation.
†Wilcoxon rank sum test.

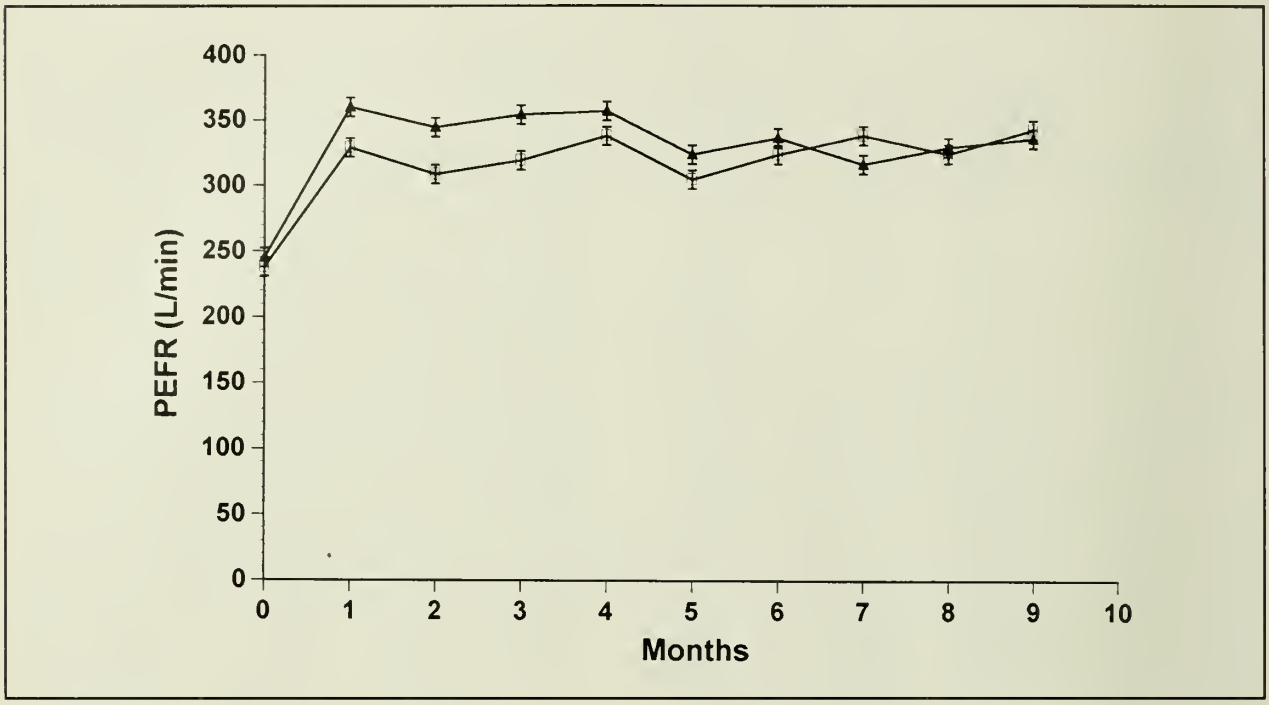

Figure 1.—Average monthly mean peak expiratory flow rates (PEFRs) during the study are compared. □, patients who received 120 mg of triamcinolone acetonide; ▲, patients who received 360 mg. There was a significant difference after 1 month ($P < 0.05$). Bars indicate standard errors of the mean.

than during the year before the study ($P < 0.02$). The average (± standard error of the mean [SEM]) cumulative dose of oral prednisone among all study patients was 4,819 ± 1,027 mg in the previous year, whereas the cumulative dose of triamcinolone required (360 mg of triamcinolone was assumed to be equivalent to 450 mg of prednisone) in prednisone equivalents was 1,014 ± 216 mg for all patients during the study ($P < 0.02$, Student's 2-tailed t test). These results suggest that steroid requirements are significantly less when high-dose intramuscular triamcinolone is used in lieu of oral prednisone in asthma patients who require maintenance systemic corticosteroids. When the two treatment groups are compared with respect to the average (± SEM) cumulative dose of triamcinolone (in prednisone equivalents) required during the study, we find that the patients who received 120 mg of triamcinolone acetonide received 990 ± 313 mg, in comparison with 1,035 ± 299 mg in patients who received 360 mg of triamcinolone ($P = 0.78$, Student's 2-tailed t test). No patient in either treatment group required a maintenance supplement of oral prednisone or any other oral corticosteroid during the study. On entry, all patients were using either triamcinolone acetonide (200 μg 4 times a day) or beclomethasone dipropionate (2 puffs or 84 μg 4 times a day) metered-dose inhalers. All patients continued to use these inhaled corticosteroid preparations throughout the study.

Steroid-associated side effects were observed in both of our treatment groups and were compared with conditions before the study, as shown in Table 3. Cushingoid facies, weight gain, and hypertension were observed less frequently after treatment with triamcinolone than at entry into the study ($P \leq 0.02$). Eleven patients, for example, had pronounced cushingoid facies at entry into the study. Cushingoid facies resolved in all but one of these patients, a patient in the 360-mg treatment group, during the study period. These observed differences in the incidence of side effects could not be correlated with either the dose of triamcinolone acetonide used in the study or history of oral prednisone use ($P > 0.06$).

The incidence of other steroid-associated side effects such as menstrual irregularities, including amenorrhea, irregular cycles, or menorrhagia; acne; gastrointestinal side effects; elevated blood glucose levels; and the incidence of cataracts remained essentially unchanged from baseline throughout the study.

Discussion

The severity of asthma varies widely among patients and even in individual patients over time. Most patients' asthma can be managed with inhaled β_2-agonists and inhaled corticosteroids, and they can lead normal lives. In some patients, however, asthma is severe and chronic. These patients have a long history of corticosteroid dependence, frequent ED visits, hospital admissions, and occasionally, ventilatory failure. A growing body of evidence suggests that both the severity of asthma and mortality associated with asthma are increasing.[13,14] If this is indeed the case, physicians may expect to see more patients with severe chronic asthma.

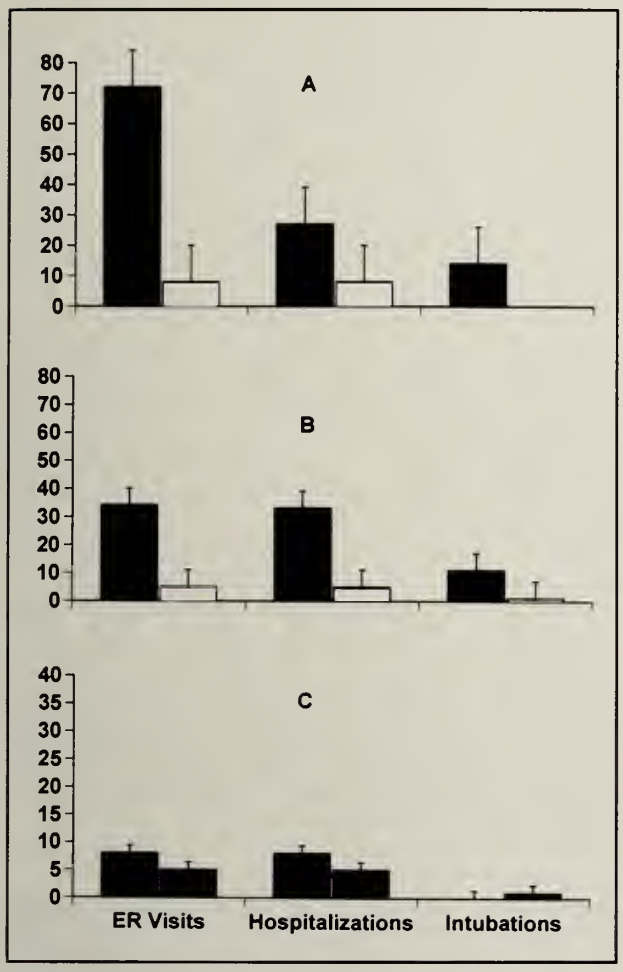

Figure 2.—Emergency room (ER) visits, hospital admissions, and intubations are shown for patients who received 120 mg (A) or 360 mg (B). The cumulative incidence is shown during the 12 months before (black columns) or after (white columns) enrollment in the study. C, the cumulative incidence 12 months after initial treatment is shown in patients who received 120 mg (black columns) or 360 mg (gray columns). Bars indicate standard errors of the mean.

The purpose of this study is to test the hypothesis that the use of intermittent high doses of intramuscular triamcinolone acetonide, as the sole parenteral corticosteroid is more effective in controlling symptoms of asthma in patients with severe chronic disease than oral prednisone. The patients selected for this study were known to have had poorly controlled asthma for an average of 24 years (Table 1), during which time they were treated with oral corticosteroids on a continuing basis. At entry, all study patients were being treated with daily oral prednisone for at least a year. The average duration of daily prednisone therapy was nine years (±6.4) at a mean dose of 14.4 mg (±5.4). Their disease was characterized by numerous hospital admissions, ED visits, and the need at times for mechanical ventilation. While two patients, numbers 4 and 16, were being treated with 5 mg per day of oral prednisone on admission, these patients had presented with severe worsening of asthma requiring ED treatment or hospital admission in the year before the study when this relatively low dose of prednisone was discontinued.

We compared two active interventions with each other prospectively, and with historical data retrospectively, in a self-controlled study design in which patients served as their own controls. We compared two doses of intramuscular triamcinolone acetonide for clinical efficacy and for the frequency and severity of steroid-associated side effects. Findings were compared with the medical history of study patients for the year before admission. We planned this study with a positive control rather than a placebo group because we felt that the use of placebo would be unethical given the severity of disease exhibited by the study patients. We considered these patients, based on our extensive clinical experience with them, to be steroid dependent with severe unstable disease and thus not appropriate candidates for a placebo-controlled study. In addition, our desire to determine the efficacy of triamcinolone acetonide use alone in these patients precluded the use of prednisone in a way that would have allowed for a prospective "placebo" design such as one used by others.[11]

This self-controlled study design is subject in particular to a bias arising from the "Hawthorne effect," in which patients change their behavior and sometimes improve simply because they receive special attention by being in a study and not as a result of the intervention itself. This special attention might take the form of regular, more frequent clinic visits once the patients are enrolled in a study, where previously there may have been only intermittent, irregular follow-up, perhaps from a number of different primary or emergency care physicians. We were aware of this potential for bias in self-controlled studies, but did not consider it to be relevant in our trial chiefly because we had been observing these patients with regular clinic visits throughout the 12-month period from which the retrospective data are drawn. This regular follow-up continued, of course, during the study, although because of pronounced symptomatic improvement following treatment with triamcinolone acetonide, patients were actually seen less frequently than during the previous year.

Both 120 mg and 360 mg of intramuscular triamcinolone acetonide reduced the severity of asthma in the study as exemplified by a significant reduction in the number of ED visits, hospital admissions, instances of ventilatory failure, and total cumulative doses of corticosteroid required when compared with oral prednisone in the year before the study. Significant improvements over baseline values in pulmonary function as exemplified by higher monthly PEFRs were observed in both treatment groups.

Although no significant difference was observed between the two treatment groups in cumulative number of ED visits, hospital admissions, and instances of ventilatory failure, patients who received 360 mg of triamcinolone acetonide had significantly higher monthly

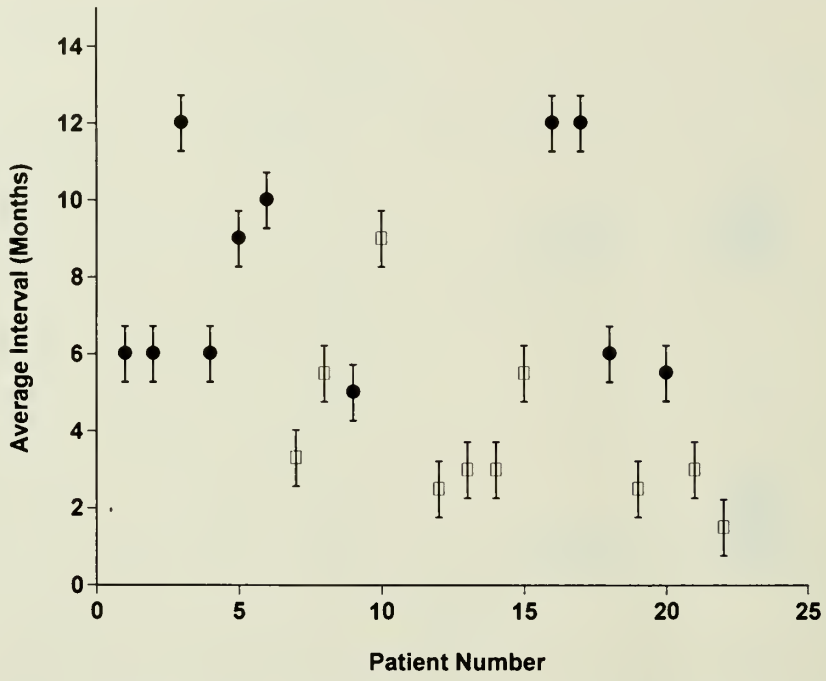

Figure 3.—The average monthly interval between exacerbations requiring readministration of triamcinolone acetonide for patients receiving either 120 mg (□) or 360 mg (●) is shown. Bars indicate standard errors of the mean.

peak flow rates and longer exacerbation-free intervals than patients who received 120 mg of triamcinolone. Some steroid-associated side effects were reduced from pretreatment levels; no steroid-associated side effects were increased in frequency or severity in either treatment group. No significant difference was observed in adverse reactions between the two treatment groups. Clinical hypoadrenalism or adrenal crisis did not develop in any of the patients. An increase was observed, however, in the number of patients from both treatment groups who showed an adrenal response. Several patients were able to return to work. These finding suggest that the higher dose of 360 mg of intramuscular triamcinolone acetonide is more effective than 120 mg in controlling the severity of asthma in patients with severe, chronic asthma while conferring no added toxicity.

The long pharmacologic half-life of triamcinolone acetonide as compared with oral steroids and other depot corticosteroids has been noted for some time.[15,16] Triamcinolone is released from the acetonide or depot

TABLE 3.—*Percentage Incidence of Side Effects During Study*

Side Effect	*Percentage*			*P Value**
	Historical Controls, n = 22	*Triamcinolone, 120 mg, n = 10*	*Triamcinolone, 360 mg, n = 12*	
Weight gain	41	0	0	0.012
Weight loss	0	20	50	0.03
Cushingoid facies	50	0	8.3	0.02
Hypertension	18	0	0	0.001
Diabetes mellitus	14	9	18	0.32
Irregular menses (*n* = 19)	14	18	9	0.32
Upper gastrointestinal distress	4.5	0	9	0.52
Acne	4.5	9	0	0.52
Skin bruising	23	20	25	0.25
Cataracts	4.5	0	4.5	0.52

*Fisher's exact test (2-tailed).

form of the drug by the enzymatic process of deacetonization. Its prolonged pharmacologic action is due in part to the slowness at which this enzymatic process takes place.[17] It is possible that high-dose oral corticosteroids might be as effective as the high doses of intramuscular triamcinolone used in our study, although the incidence and severity of some steroid-associated side effects would probably increase based on our experience with this study. Depot preparations have the added benefit that the clinician knows that the patient has received a corticosteroid. Compliance factors do not enter the picture.

Some physicians may be reluctant to use intramuscular injections of corticosteroids because of the perception that injection-related side effects might be a problem. Dermal atrophy can occur at the site of steroid injections, but the risk of subcutaneous atrophy can be reduced by giving the injection in the gluteal area, avoiding leakage of solution into the dermis.[18]

Thus, in a self-controlled study in steroid-resistant patients with severe chronic asthma, high doses of intramuscular triamcinolone acetonide lowered the cumulative dose of corticosteroid required; reduced the number of ED visits, hospital admissions, and intubations; improved pulmonary function; and enhanced patients' quality of life when compared with low to moderate doses of oral prednisone. Some steroid-associated side effects decreased in incidence. The higher dose of 360 mg promoted higher monthly peak flow rates and a significantly longer symptom-free period with no increase in adverse reactions over the 120 mg group. Our findings are consistent with the views expressed by previous investigators[7–9,11] that intramuscular triamcinolone acetonide is a potentially valuable alternative to oral corticosteroids in the control of severe, chronic asthma.

A follow-up investigation using a double-blind positive control model appears warranted to enhance the objectivity and reliability of the outcomes measurements. A procedure for maintaining the blind could be devised using the services of an investigational pharmacist and research nurse. One treatment group could receive a single injection of triamcinolone acetonide, 120 mg, followed by the administration of saline solution on the two following consecutive days. Patients in the second treatment group could receive single injections of triamcinolone acetonide, 120 mg, on three consecutive days. Exacerbations would be treated with additional triamcinolone acetonide appropriate to the treatment group, administered as a three-day course by the study nurse and recorded by the research pharmacist. We do not feel that a crossover model is appropriate given the clinical characteristics of this group of patients and our desire to exclude oral prednisone from the study design.

ACKNOWLEDGMENT

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Articles

Geographic Distribution, Supply, and Need for Generalist Physicians in Alaska

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This study provides the first comprehensive description of Alaska's geographic distribution of generalist physicians relative to population. All 443 generalist care physicians (family, general, general internal medicine, and pediatric) or their office managers were questioned about their specialties, ZIP codes, employers, populations served, and hours spent per week offering direct patient care. The results indicated a 30% overall shortage of generalist physicians for the state, representing roughly 141 full-time-equivalent generalists relative to national practice patterns and trends of health maintenance organizations. Of 17 primary health care areas, including the Anchorage area, 15 showed a need for additional generalist physicians. Most areas had a 20 to 40% shortage. Concerns about transportation and financial barriers to access to care, especially in remote regions, were raised. Other needs emphasized included knowledge of contributions of midlevel health care professionals, Alaska Native versus non-Native care, efforts to train and retain physicians in Alaska, and the need for longitudinal tracking of practice patterns.

(Johnson DR, Norris TE. Geographic distribution, supply, and need for generalist physicians in Alaska. West J Med 1997; 167:330–335)

Encompassing 586,412 sq mi, six major mountain ranges, two time zones, and more active glaciers than anywhere else in the inhabited world, Alaska is a land of raw beauty and vast distances. With a total population of 550,038, including an indigenous population of 86,123,[1] there are fewer than 1 person per sq mi in Alaska, compared with 70 persons per sq mi in the rest of the United States. In 1994 there were 240,258 people living in Anchorage, the state's largest city and only metropolitan statistical area. The combined populations of Anchorage, Fairbanks, and Juneau, the three main urban centers in Alaska, account for 61% of the state's population. The remaining population lives in rural, or "frontier," communities frequently separated by large distances and geographic barriers.[2]

Alaskan residents can be categorized into three patient populations cared for by largely separate health care systems: Alaska Native, non-Native (nonmilitary), and military. The agencies providing health care services for Alaska Natives include tribal health corporations and the Indian Health Service. In remote villages, community health aides treat minor ailments or refer patients from the village clinic to a hospital under the telephone guidance of a physician.[2] The 400 community health aides in Alaska are chosen by village councils and are often the first point of contact for many rural, and especially Native, patients.[2,3] Health care for non-Natives and military personnel is provided through private physicians and organizations, military personnel, and in the case of Alaska's most northern regions, the North Slope borough. In addition, the state's public health nurses provide a variety of services to Alaska residents throughout the state, including those in remote communities.

Despite the three delivery systems cited, evidence provided in several state and national studies suggests that many geographic areas in Alaska are medically underserved and do not have adequate access to basic health care services.[2,4–9] In 1993, Alaska had 20 federally designated health professional shortage areas and 10 medically underserved areas. These shortage areas encompassed a third of the state's population and two thirds of the state's land area.[4] Previous investigations did not specifically investigate primary care, did not have adequate response rates, or did not look at the geographic distribution of physicians.

At the same time that Alaska's shortages have been noted, the entire nation has been struggling with ques-

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ABBREVIATIONS USED IN TEXT

ADPH = Alaska Division of Public Health
FTE = full-time equivalent
HMO = health maintenance organization
PHCA = primary health care area
WAMI = Washington, Alaska, Montana, and Idaho

tions of whether we have enough physicians, what would be the optimal mix of specialties, and what is the best geographic distribution of physicians. How to determine "how many is enough" and how to project whether there will be a surplus or deficit in the future are still hotly debated. Several major investigations, starting with the findings of the Graduate Medical Education National Advisory Committee, have predicted that, at current levels of physician training, there will be a large future surplus of physicians compared with need (or demand).[10–15] Estimates of the degrees of the surplus vary greatly depending on the underlying assumptions. The most recent studies have based projections on the staffing patterns of health maintenance organizations (HMOs), suggesting that there will be a surplus of specialist, not generalist, physicians or that perhaps there will not be a gross surplus of physicians at all.[10–14,16]

Even studies that assert future "surpluses" agree that physicians are maldistributed, resulting in persistent shortages of health professionals for rural populations, certain ethnic groups, and other economically disadvantaged populations, despite an increasing supply of physicians.[13–15,17,18] From 1975 to 1985 the number of physicians per 100,000 people grew three times faster for the United States as a whole than for rural areas.[19] The "trickle-down" theory that as physician supply increased, market forces would push physicians into underserved rural areas, has not occurred.[11,12,15,20,21]

The 1995/1996 edition of Physician Characteristics and Distribution in the United States notes few improvements from 1980 to 1994 in the United States in rural primary care practice: the total percentage of physicians practicing family or general medicine declined slightly from 10.8 to 8.8%, and the percentage of family physicians in rural areas declined from 25.6 to 21.1%.[22] One investigator projected that ten states, including Alaska, will have a possible net loss of primary care physicians by the year 2002.[23] This phenomenon may be due to the retirement of an older generation of primary care physicians, without adequate replacements. The finding that Alaska ranked 48th of the 50 states in 1994 for overall number of nonfederal patient care physicians per 100,000 residents is cause for concern.[22]

Cunningham and Cornelius indicated that the methods of previous studies may have obscured access barriers encountered by American Indians and Alaska Natives.[24] They found that the "availability of medical care providers, as well as location of residence, were [sic] strongly associated in the use of health care by American Indians and Alaska Natives."(p 393) Travel times were substantially longer for people living in rural areas with few health care professionals, and fewer hospital admissions were reported in areas where Indian Health Service outpatient services were close by. Financial factors also were important in predicting health care use outside of the Indian Health Service.[24]

There are no concrete data characterizing primary care physician supply, or distribution, in Alaska relative to the population. The purpose of this study was to provide specific data on the number and geographic distribution of Alaska's generalist physicians within functional health care areas both for Alaska Natives and non-Natives. The central study questions were as follows:

- What is the geographic distribution of generalist care physicians in Alaska?
- What are the generalist physician-to-population ratios in various health care areas of Alaska relative to standard ratios used in the rest of the nation?
- Is there a difference in generalist physician-to-population ratios for Alaska's Native population versus its non-Native population?

Methods

Physician Variables

"Primary care physicians" were defined as all medical or osteopathic family practitioners, general practitioners, general internists, and pediatricians. Physicians were identified primarily from the 1995 Medical Directory of the Alaska State Medical Association.[25] The directory is updated yearly and based on information obtained from local professional groups throughout the state. This was supplemented with information provided by the Alaska Division of Public Health (ADPH), Section of Community Health and Emergency Medical Services, and conversations with hospital and clinic personnel about new physician losses and gains within their organizations and geographic locations. Because many communities in Alaska are small and are served by only one or a few health care facilities, this process is thought to provide accurate information. The American Medical Association's masterfile was not used because of concerns that a lag in updating could be misleading in sparsely populated communities where an error of a few physicians would be critical. State licensing rosters were also not used, since a substantial number of physicians licensed in Alaska do not practice or live in the state.

In conjunction with the ADPH's Section of Community Health and Emergency Medical Services, all of Alaska's 443 primary care physicians—or their office managers or hospital administrators—were interviewed by telephone during the spring and summer of 1995. Interviewees included physicians in all sectors of health care delivery: private, Indian Health Service, tribal, borough, veterans, and active military. Physicians were asked the following five questions:

Table 1.—*Population, Physician Full-Time Equivalents (FTEs), and Shortage Findings for Each Primary Health Care Area (PHCA)*

PHCA Name	Total Population	Actual Total Generalist Physician FTEs	Expected Total Generalist Physician FTEs*	No. of Generalist Physicians Short*†	Percentage Shortage of Generalist Physicians*†
Barrow	5,069	6	4.22	1.78	42.04
Kotzebue	6,751	3.24	5.63	−2.39	−42.41
Nome	8,311	5.29	6.93	−1.64	−23.62
Bethel	20,222	5.31	16.85	−11.54	−68.49
Kodiak	13,308	10.87	11.09	−0.22	−1.98
Prince William	7,141	4.62	5.95	−1.33	−22.36
Kenai Peninsula	41,089	21.41	34.24	−12.83	−37.47
Anchorage	226,202	107.92	188.50	−80.58	−42.75
Matanuska	39,649	24.43	33.04	−8.61	−26.06
Fairbanks	90,980	65	75.82	−10.82	−14.27
Dillingham	6,381	3.65	5.32	−1.67	−31.36
Glennallen	2,811	1.51	2.34	−0.83	−35.54
Southeast	68,286	57.26	56.91	0.35	0.62
Aleutians	11,760	0	9.80	−9.8	−100
McGrath	718	0	0.60	−0.6	−100
Yakutat	703	0	0.59	−0.59	−100
Iliamna	657	0	0.55	−0.55	−100
Total	550,038	316.51	458.37	−141.86	−30.95

*These numbers are based on an expected physician-to-population ratio of 1:1,200.
†Negative numbers indicate estimated shortage. Positive numbers indicate more than expected.

- What is your specialty?
- Who employs you?
- How many hours per week do you provide direct patient care, excluding emergencies, hospital care, on-call time, vacation, and administrative duties?
- If you work for a Native organization (Indian Health Service, borough, or tribal), what percentage of your patients are non-Native?
- What is your practice ZIP code?

Responses concerning hours were either verbal or faxed in the form of physician schedules.

Population Variables

Population data were obtained from the Claritas Corporation, which bases its population estimates on yearly updated census bureau estimates. Native and non-Native population totals were obtained for every ZIP code in Alaska.[1]

Geographic Variables

A total of 17 primary health care areas (PHCAs) were developed in consultation with the ADPH's Section of Community Health and Emergency Medical Services, based on their knowledge of utilization patterns—that is, where residents of a particular community and ZIP code predominantly go to receive primary care. Every ZIP code of a physician's practice location and patient residence was located within one of these areas.

Analyses

Descriptive statistics were used to compare the variables of interest among primary health care areas. The number of "full-time-equivalent" (FTE) physicians was calculated for each PHCA. We defined 34 hours or more of direct patient care per week as constituting one FTE. This criterion was based on national averages reported in Socioeconomic Characteristics of Medical Practice 1993 for the number of hours generalist physicians considered to be "full-time" actually spend per week providing direct patient care outside of the time they spend fulfilling other duties such as paperwork.[26] This criterion was thought to best represent the number of hours a physician is available to patients and would tend to err on the side of overestimating rather than underestimating physician supply. The FTE shortage was calculated by subtracting the number of expected FTEs for an area's population from the number of actual FTEs. One physician per 1,200 people was the standard used to calculate expected FTEs. Washington State also used this ratio as a standard in its health personnel needs assessment as based on findings in FACTBOOK Health Personnel United States (US Department of Health and Human Services, 1993)[27] and HMO Industry Profile, 1993 edition.[28] The 1:1,200 ratio was expected to be adequate for both rural and urban areas.[29] Map Info, a database mapping program developed by the Map Info Corporation of Troy, New York, was used to display the degree of shortage within each PHCA.

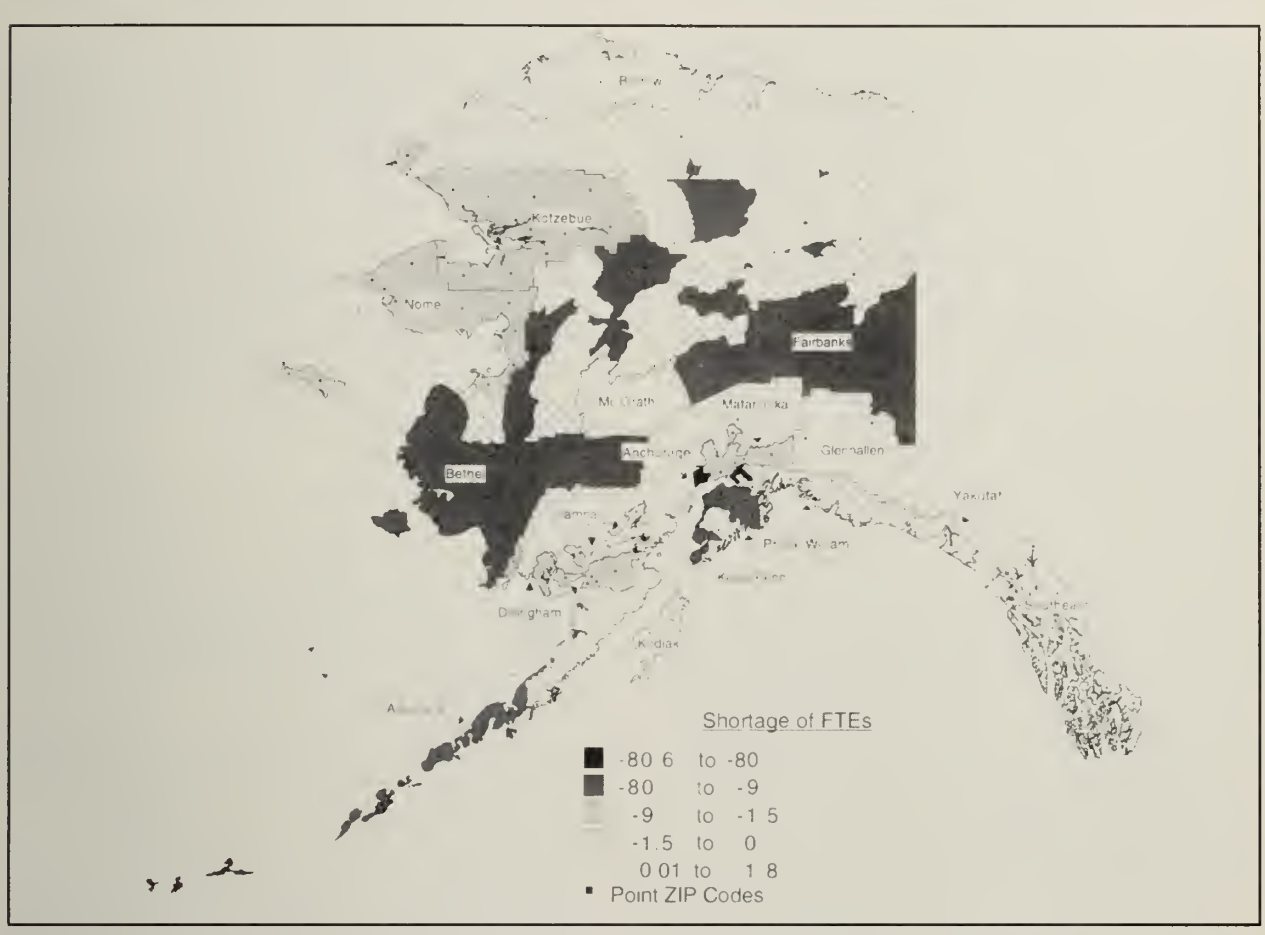

Figure 1.—Alaska primary health care service areas are shown by shortage in physician full-time equivalents (FTEs). (This map was produced by the University of Washington, Rural Health Research Center, 1996. The health service areas are based on 1994 ZIP code areas. Principal Investigator: Deanna Johnson. Cartographers: Mary-Katherine Goodwin and David Felt.)

Results

Table 1 shows population, generalist FTEs, and estimated shortage findings for each PHCA. These results represent a 100% response to the question of ZIP code location of practice, a 99% response rate to the question concerning physicians' specialty, and a 98% response rate concerning hours per week spent offering direct patient care services. All but 2 of the 17 PHCAs demonstrated shortages of generalist physicians, as indicated in Table 1 and illustrated according to degree on the map of Figure 1. Overall, there was a generalist FTE-to-population ratio of 1:1,728 (58/100,000) in Alaska compared with the national standard of 1:1,200 (83/100,000). When the Anchorage PHCA was excluded from the analysis, the ratio was 1:1,552 (64/100,000). The Anchorage PHCA lacked the largest absolute number of generalist FTEs, with an estimated 80 FTE deficit. The state had a 30% generalist FTE shortage overall, representing an approximate total of 141 FTEs. Most areas showed a 20 to 40% deficit. The Bethel PHCA was the exception, with a 68% deficit from expected generalist FTE totals (although, for reasons mentioned in the discussion, Bethel's shortage was most likely overestimated). The response rates to the questions concerning employer and percentage of time spent serving Native versus non-Native populations were 59 and 26%, respectively, and therefore could not be adequately analyzed within each PHCA.

Discussion

The evidence provided by this study suggests that Alaska has a striking shortage of generalist physicians compared with national standards of adequate physician-to-population ratios. Moreover, the scarcity of physicians was geographically universal for most populated areas (see Table 1 and Figure 1). Rural areas (outside of Anchorage, Fairbanks, and Juneau) showed shortages, but because of the smaller populations in some of these areas, the addition of just a few physicians would noticeably improve the ratios. Although it is inappropriate to use physician-to-population ratios to determine an absolute number of physicians needed in an area,[30] the geographically described data here point to a substantial degree of need in which relative comparisons among various locations can be made.

Even the Anchorage PHCA, the most "urban" area in Alaska, showed a 42% shortage (approximately 80 FTEs) of generalist physicians, which was higher than the overall 31% for the entire state. In this sense, the hypothesis that mainly rural areas were facing physician supply issues was not supported. Could specialists in Anchorage be compensating for this shortage by practicing primary care as well as specialty care? This is unlikely given that Anchorage, the major specialist referral center for the state, also has a notable shortage of specialists compared with other urban specialty referral centers in the United States.[22] It would be useful to compare Anchorage's apparent primary care shortage with that of cities of similar size in the Northwest. Unfortunately, data on primary care physician availability in cities such as Spokane (Washington), Salt Lake City (Utah), and Boise (Idaho), derived from the same method used in this study, are not available. This would be an excellent area for future study.

The shortages indicated in this study could be conservative estimates because 34 hours spent in direct patient care office visits was defined as equal to 1 FTE and because physicians close to retiring were not excluded. Many telephone conversations while gathering data revealed that some physicians actually worked 50 to 70 hours plus per week. National trends demonstrate that rural physicians consistently have more patient visits than their suburban or urban colleagues.[31] Although this aspect was not specifically investigated in this study, it raises the possibility that the degree to which more physicians are needed in some areas could be different than indicated here.

A factor that makes solving rural physician supply problems in Alaska especially difficult is that many areas such as McGrath, Yakutat, and Iliamna are not large enough to support a physician. The critical mass of residents that can financially support a private physician is usually considered to be higher than optimal physician-to-population ratios.[31] In addition, transportation barriers to health care in rural Alaska are monumental, given that many communities are widely dispersed and isolated. Excluding the more populated areas with road systems and shorter travel distances, it will be of little benefit to bring in additional physicians if people cannot, or will not, use them because of the financial and logistical transportation barriers. Unmet health care needs in these areas may be high, but the actual demands for services are lower than expected because of the realities of community isolation. Information about the midlevel practitioners and their geographic distribution in locations with and without physicians will further clarify primary care availability and access challenges. Whereas this study focused on physician-provided primary care, a similar data set should be developed for non-physician–based primary care. This new information should be integrated with this study to provide a clearer total picture. Additional limitations of this study include the following:

- Generalist FTE shortages could not be analyzed separately among Alaska Native versus non-Native populations within each PHCA. Physician response rates to the question concerning percentage of time providing for Native versus non-Native populations were inadequate and inconsistent among the areas.
- This study specifically asked about hours per week spent providing direct patient care in an office or outpatient setting. It therefore did not include primary care offered in other settings such as emergency departments. This appeared to be more of an issue with remote hospitals serving isolated Native communities, such as the hospital in Bethel. A more detailed analysis of how primary care is provided in these areas is needed.
- Midlevel practitioner and community health aide contributions were not included in this assessment of primary care distribution and shortage. Efforts by ADPH's Section of Community Health and Emergency Medical Services and the Washington, Alaska, Montana, and Idaho (WAMI) Rural Health Research Center are ongoing to investigate these physicians' practice patterns and geographic distributions.
- The effects of transportation costs and travel patterns on access to primary health care were not investigated.
- Data were often collected from office managers and hospital administrators instead of physicians themselves because of the difficulty in reaching physicians directly. This was not thought to be an important factor given that office managers oversee scheduling and know when patients are being seen.
- Physician numbers fluctuate with time. These data were collected over the spring and summer of 1995, over which time physician numbers could have shifted.

Ultimately the question is how much does Alaska's apparent deficit in primary care physicians contribute to decreased access to basic health care for its residents. Cunningham and Cornelius found that a decreased availability of physicians and facilities was an important contributor to decreased use of ambulatory care for Alaska Natives.[24] The severity of Alaska's shortage suggested here indicates that it is probably a sizable contributor. Frenzen, however, emphasized that decreased physician-to-population ratios do not necessarily mean that there is unequal access to care because rural residents may "cross over" areas to receive care in more urban locations.[15] Anecdotal evidence indicates that people in "bush" Alaska fly to cities like Anchorage to receive health care. Anchorage, Fairbanks, and Juneau are the only cities where specialty care is available, and Alaskans may go there for primary care as well. The fact that Anchorage was shown to have a shortage of generalist physicians and that flying to Anchorage often involves hundreds of miles and costly airfares may make this an irrelevant point for Alaska. It is more likely that

rural residents often fail to seek medical care, especially consistent primary care.

Based on this study, further investigation is needed in several areas to completely understand Alaska's shortage in primary care. These areas include the following:

- Transportation and distance issues as a barrier to providing primary care.
- The role of other primary care professionals (community health aides, physician assistants, nurse practitioners, certified nurse-midwives) in providing care in Alaska. (A recent study indicates that mature HMOs have not replaced primary care physicians with midlevel practitioners but employ high levels of both.[10])
- Native versus non-Native access to primary care services in Alaska.

This study indicates that Alaska needs more primary care physicians in both rural and more populated areas. This objective might be accomplished in several ways. MacGregor Potter[32] and others[17,33,34] have shown that the opportunity for rural exposure during medical training is a predictor of future rural practice. Programs such as the WAMI medical program, offering such exposures and encouraging primary care practice in general, need to be supported. Loan repayment or forgiveness programs could also attract primary care physicians to Alaska, given that most medical students are substantially in debt by the time they graduate and that primary care employment generally pays less than employment in a medical specialty.[12,33] Factors that increase retention also need to be investigated and addressed.[32]

Conclusion

This study provides evidence that generalist physician shortages exist rather uniformly throughout Alaska when compared with accepted national and HMO generalist physician-to-population ratios. Alaska's unique transportation barriers offer additional complexity. There is a critical need to work toward both increasing the supply of physicians for all residents and improving the ability of health care professionals and patients to travel to each other in a timely, cost-effective manner.

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Articles

Closer to Home (or Home Alone?)

The British Columbia Long-Term Care System in Transition

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Finding ways to organize and deliver long-term care that provides for quality of life at an affordable price is of increasing importance as the population ages, family size decreases, and women enter the workforce. For the past 2 decades, British Columbia has provided a model system that has apparently avoided disruptive conflicts. Although formal users' complaints are rare, this study—based on focus groups and interviews with users, their families, and advocates—identified problems users encountered toward resolving concerns about the structure, process, and outcome of long-term care. We present these findings in the context of British Columbia's current devolution from provincial to regional control that aims to save costs and keep disabled elderly persons in the community. British Columbia may be continuing to lead the way in meeting the needs of its burgeoning elderly population for long-term care. Study findings have implications for the development of US long-term care policy by pointing to the value of obtaining users' views of long-term care to identify both obvious and more subtle trouble spots.

(Brody BL, Simon HJ, Stadler KL. Closer to home (or home alone?)—the British Columbia long-term care system in transition. West J Med 1997; 167:336–342)

The world's population is aging. The consequent growth in the number of disabled older adults demands that attention be focused on new approaches to address their health and long-term care needs. The widely and justly admired Canadian long-term care system, as exemplified in British Columbia, is now in transition. In this article, we analyze the changes under way and discuss users' concerns about quality.

The Canadian population, like that of the United States and most of the industrialized world, is aging. The number of those aged 65 and older has been increasing throughout this century. Currently they make up 12% of the Canadian population. By 2021, they are expected to make up more than 20% of the population. About 45% will be the "old elderly," those aged 75 years and older.[1] Between 1990 and 2000, the 75- to 84-year-old group will have increased by 36%. The number of those aged 85 and older will have increased by 51%.[2]

In British Columbia, the over-65 population is anticipated to increase to 16.2% by 2011 from 12.8% in 1988. Of this increase, 12% will be the group older than 85.[3] Not only will there be more seniors in the population, but the seniors themselves will be older.

This demographic shift will surely affect long-term care in British Columbia. Altogether, these trends show the salience of the discussion about reform of the long-term care system. Regardless of the direction in which the long-term care system is pushed—toward the community, institutions, or elsewhere—it is likely to undergo greater stresses and will be asked to meet more demands.[1] Some have advanced the notion that older people will in the future be healthier.[4–7] They suggest that the period of morbidity will be compressed and the need for long-term care lessened. Others, however, hold that the large number of persons reaching advanced age will also include, at least for the foreseeable future, a greater number of disabled elderly who will require long-term care services.[8,9]

The authority over and responsibility for health care once held by the provinces are being devolved to smaller jurisdictions. Thus, British Columbia has been divided into 21 regions. Each is governed by a regional health board (RHB) whose members are appointed by the Minister of Health. Each RHB must set priorities, develop policies, and allocate resources for itself. Within the RHBs, community health councils (also composed of

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Ministry-appointed members) then become responsible for providing services.[10] Whereas a hierarchy for regionalization has been established, the extent of each board's authority, the adequacy of its budget, and the directions of its policies and priorities are still unclear.

British Columbia has recently launched new initiatives that emphasize what has hitherto not been addressed in great detail; namely, the consumer's view of the system.[11,12] Conflicts are bound to occur in interactions wherein the various parties at interest manifest different motivations, incentives, expectations, and values. The identification of problems and their relative importance may also vary, as may the views on how problems are resolved. Our earlier study found that providers of and payers for continuing care services tend to resolve conflicts in the organization and delivery of continuing care services through negotiation and accommodation, and impasse is rare.[13] Further, users of services rarely seek satisfaction with problems in continuing care through lodging formal complaints or legal recourse.

The purpose of this inquiry was to identify problem areas encountered by users and their advocates and their satisfaction with the resolution of these problems.

Background of Reform: The Basics

The evolution of the Canadian acute and long-term care benefits has been the focus of previous research.[13,14] The Canada Health Act provides for a system of universal health insurance financed by taxes and administered by the provinces. It assures access to all medically necessary hospital and physician services in any province without payment by the user at the point of service; it is a central part of the three-pronged approach to long-term care in Canada. The Canada Assistance Plan and the Canada Pension System provide for income maintenance for both poor and elderly persons. The federal government permits provincial autonomy in the implementation of long-term care responsibilities. British Columbia features a case-management, single-point-of-entry system into long-term care. Persons wanting care beyond the case-management allocation can purchase such care privately, although few do so. Medically related long-term care services and case management are covered without payment at the point of services. Some charges are allowed for home care and for room and board in long-term care facilities, with the amounts determined on a sliding scale.[13]

In the late 1980s, several Canadian provinces began to reevaluate their health care systems. In 1989 the British Columbia Department of Health produced "Toward a Better Age," a report detailing 21 recommendations to improve health care in the province.[15] For long-term care, the recommendations focused on shifting the emphasis from facilities to in-home services, promoting preventive programs, helping caregivers, and increasing the availability of nursing home beds in small communities, especially the number of beds available for persons with special needs. In 1991, although the British Columbia Royal Commission on Health Care and Costs approved the 1989 recommendations, it emphasized more effective use of existing resources over incurring additional expenses.[15]

As the foundation for change, several themes relating to long-term care emerged from the Commission's report. The most prominent were regionalization and an emphasis on community-based over institution-based care. The Commission singled out three principles to guide the coming changes. The first states that long-term care facilities should be homelike; people should feel like residents and not like patients. The second states that people residing in facilities should live near their family and community. The third principle states that a sufficient number of long-term care beds should be available to avoid increases in the costs of acute care. The Commission also emphasized the importance of administrative features, such as case management and single point of entry, which have characterized long-term care in British Columbia since the early 1980s.[2]

The goal of Canada's broad spectrum of long-term care services is to enable elderly persons to "age in place." Remaining at home and maintaining personal autonomy are at the heart of this concept. As a result of the extensive support system of services, both informal (unpaid) and formal (paid), most Canadians are indeed able to remain at home.[1] This translates into savings of funds that the government would otherwise have to use to pay for institutional care. Some of these savings are returned to users in the form of tax credits (designed to further assist them to remain at home).

To help more Canadians to "age in place," the federal government in 1991 expanded the qualifiers for the medical expense tax credit to include specific items that promote independence, such as home modifications for people with severe and permanent mobility restrictions.[1]

In that year, the federal budget also extended tax assistance (up to $5,000 in deductions) to disabled taxpayers and their families who pay for part-time attendant care, including the costs of respite care. Because families are expected to care for their elderly members, this portion of the tax credit expressly requires that the attendant not be related to the disabled person.[1]

Methods

We intended to explore the key items of users' perspective around which conflicts might occur in the long-term care system. Consequently, in the summer of 1996, we conducted a series of semistructured interviews and focus groups with 47 users of long-term care, family caregivers, and advocates for the elderly in British Columbia. A total of 14 persons were interviewed and an additional 33 persons participated in one of four focus groups consisting of six to ten persons each. Through a systematic inquiry of governmental and private sector organizations serving elderly and disabled persons, these individuals were identified as representative and articulate users or advocates of long-term care

in urban, suburban, and remote areas of Vancouver and Victoria. Each participant in this study was identified by more than one source as being an appropriate informant. Concerns were conceptualized according to Donabedian's widely used construct of quality[16] along the dimensions of structure (access to appropriately located and staffed services), process (provision of the appropriate amount and types of care), and outcome (improvement in health and function and patient satisfaction or, in the case of long-term care, less decline than expected).[14] All interviews and focus groups were conducted by one of us (H.J.S.) using a protocol of questions that had been sent in advance to participants (protocol available from the authors on request). Focus groups were homogeneous in that all had direct experience with long-term care services in British Colombia. The protocol was designed to systematically elicit users' views[17] of the continuing care system in terms of the domains of the structure of the continuing care system (satisfaction with the kinds of facilities, providers, amenities, access, complaint mechanisms), satisfaction with the process of care (single point of entry, nature and amounts of care, interpersonal aspects of care, the manner in which complaints are addressed), and satisfaction with outcomes of care (resultant health status, resolution of conflicts, changes in expectations).

All sessions were tape recorded, transcribed, and then reviewed and edited. Two of us (B.L.B. and K.L.S.) independently classified the responses in accord with the three domains using the protocol as a guide to identify themes. When two or more respondents expressed similar concerns, a subtopic was created within one of the three domains and representative illustrations selected. Raters agreed in about 75% of the classifications. Disagreements were resolved through discussion and eventual consensus among all authors.

Results

Clients' and advocates' overriding sentiments, frequently reiterated, indicate general satisfaction with long-term care in British Columbia. Complaints were elicited primarily in response to specific questions and invitations and were usually couched in terms of recent developments when compared with the situation in the early 1990s.

Figure 1 presents a qualitative pattern of concerns that emerged in accord with case-based information derived from focus groups and individual interviews.

Structural Issues

Structural issues centered mainly around staffing patterns, especially as related to the allocation of services. To a lesser degree, concerns about institutional design features and complexities involving the complaint process were also mentioned.

Process

Regarding the process of long-term care, users expressed concerns about the coordination of long-term care services, providers' and institutional sensitivity to cultural factors and personal privacy, difficulties in obtaining information about system components, and the identification of foci of responsibility at diverse levels within the system.

Outcomes

Users and advocates did express some concerns about outcomes. They appeared hesitant and voiced fears about possible adverse consequences to themselves if they were to register complaints. The principal areas of users' concerns involved separation from family; caregiver stress; and in rare instances, abuse, both physical and economic.

Discussion

As British Columbia's long-term care system evolves from emphasizing institutional care and centralization at the provincial level to a more dispersed, regionalized system of community- and home-based services, we find that users, family members, and their advocates, although generally satisfied, voice some concerns about the quality of long-term care in terms of how it is organized and provided and about outcomes.

Studies of user satisfaction with long-term care are limited in scope and number. One study of the US channeling demonstration of home care services suggested that users' satisfaction increased when any formal service was provided. Additional services resulted in only marginal increases in user satisfaction.[18] Our focus group findings are in agreement. Whereas users expressed complaints about how much care was provided, who provided it, and where it was provided, expressions of gratitude for any care at all were prominent throughout. As one interviewee said, theirs is not a generation that complains. As a consequence, users and their families have accommodated to what has been made available to them. Thus, the major mode of resolving conflicts seems to be user accommodation to whatever is provided, instead of negotiating with service providers or government to recognize, address, and resolve problems.

Potential of Community-Based Care

The central hypothesis for the emphasis on basing long-term care in the community is that living at home is virtually always preferable to living in an institution.[19] Further, proponents contend that even if the cost of a day of community-based services is equivalent to the cost of a day of services in a facility, funds will be conserved because most clients do not use community-based services on a daily basis. Accordingly, the costs of care for someone using community-based services for five days a month would likely approximate a sixth of the costs of a month of care in a facility.[20]

The extensive infrastructure and case management that characterize British Columbia's long-term care system are seen as helping the province overcome the bar-

Structure

Institutional Care

Shortages of staff for personal care. "By the time the people who need help to feed themselves get that help, their food is cold. And you can follow that right through the care process during the entire day." "By persevering, I was able to convince them to help me take a shower twice a week instead of the usual once a week. I used to shower the first thing every day."

Shortages of storage space. "One problem we've all had is not sufficient wardrobes."

Overbureaucratization. Complaints summarized as follows: complex complaint process: notify the lodge nurse—appropriate person—unit manager—loop with social worker—social worker sends you to lodge nurse—social worker's letter—Director of Lifestyles and Community Services—department heads—chief executive officer—the Board—ombudsman or Veterans Affairs or Member of Legislative Assembly.

Community Care

Severe shortages of home care personnel on weekends. "The frustration for us was that the home care services were only provided Monday to Friday. And if our family hadn't been around, he would have been institutionalized." "The weekends are chaotic.... Everything works on a skeleton staff."

Turf issues between agencies, ministries, professions. "It's utterly ridiculous that a homemaker, who is intelligent, is forbidden to carry medications to a sick patient at home. There are things called territorial warfare that have to be settled."

Not enough allocation of government-paid hours for home care. "I needed help with bathing at one time. Of course, they didn't allow it, and they cut me off for 6 or 9 months. I nearly slipped in the bath once.... Then they brought me back." "My mother developed Alzheimer's disease quite rapidly. Initially she had homemaker service, but it only went for 2 hours, 3 times a week. So, although it appeared that she had care, she had not enough care at all. I could not get the hours increased, which was a problem. Then it was time to have her institutionalized."

Rigid formulas for government benefits. "We discussed the inflexibility of the funding formula with the ministry concerned. If one is going to promote closer to home, one is going to have to take this into consideration—what the individual's situation is financially as it relates to day-to-day costs and expenses and the individual's health. If our family hadn't subsidized his care, he wouldn't have been able to cope."

Unionization: seniority is everything. "It means that you don't necessarily retain and promote those people who are most capable."

Changes with decreased funding. "We had all hoped that when there were cutbacks in the acute care, that money would come to the community, to make home support work. But it hasn't happened."

With 'closer to home,' bed reductions and reductions in paid-for benefits, qualifications of attendants, and level of services offered. "During the past 2 years, the government said that they were going to provide care closer to home. While they cut funds for hospitals, they also cut qualifications and levels of service for home support. They've realized that the people who are staying at home are in need of greater levels of care, and they restricted the amount of money that goes there. So, some people have been cut off or virtually cut off from the hours that they were [previously] entitled to."

Process

Institutional Care

Personal food preferences sometimes ignored. "My husband was there for 4 months, and he never filled out a menu. Many times he had absolutely no choice at all."

Privacy issues: knock before entering. "We should have locks on the door. . . . I find it inconvenient in that I have been personally caught a couple of times. I'm getting dressed, and somebody flies the door open, and it's the lady to come in and wash your floor. And here I'm standing in my shorts. I've been in this facility for 14 months, and still I've gotten no response."

Overuse of medications to control behavior. "My mother was an Alzheimer's patient. She was medicated without my consent. By the time I knew she was on medication, it was too late to turn back. And, frankly, the system blew her mind."

Unionization inactivates informal complaint mechanism because management is afraid of strikes if they put on any pressure. "Management in hospitals is afraid of the staff.... I don't think they talk to the staff. They're scared of the staff because they're unionized."

Community Care

Insufficient coordination for home care. "Closer to home situation ... was not as coordinated as I would like to see it. The key person identifying my husband's needs was a homemaker. If she saw a need, she had to report to her supervisor, who would then hopefully report to the supervisor at the home-care nursing program, who was in a separate building and in a separate bureaucracy, who would then hopefully report that need to the home-care RN, who hopefully within the next week or so would visit, and who never saw the homemaker. The RN came in the afternoon, the homemaker in the morning."

Cultural and language incompatibilities with caregivers. "They are not well-paid individuals. Sometimes there are communication barriers, language differences that can make it more difficult."

Lack of information about rights, privileges, appeal mechanisms for complaint resolution in some institutions and in home care. "I tried to resolve my complaint, but I was not aware of an appeal process to follow." "I don't think anybody really knew the route to getting my problem addressed. None of the professionals I was dealing with knew. It's because we are in such transition now with our health care system." "As the caregiver, I found it frustrating to be shut out concerning my husband. I couldn't get information out of any member of the team except the homemaker. I got zilch. They excluded me." "It's difficult to even find out what services are available." "What's tragic is that there is a detailed process to deal with complaint resolution, but it's not always followed."*

Hard to be an advocate. Who should be an advocate? A voice for seniors. "What happens within [British Columbia] is, we get a perpetual referral system. Passing the buck." "At present there are no seniors' advocates for community care." "Once there were community forums. They were held at 7 PM at night. You want to talk about something in the winter, in the middle of winter, that effectively cuts out seniors from participating. There were few seniors there. Only a couple of extremely committed individual seniors at the meeting. It speaks more to their perseverance, rather than to a system that allows people to talk openly and identify their problems."

Figure 1. Examples of long-term care users' concerns are given here *(continued on page 340).*

riers to making community-based care cost-effective. Thus, in-depth case management to target and match clients with the most appropriate and efficient services, together with a single point of entry, can prevent people who do not need them from receiving community-based services.[1,20]

Community-based care has traditionally been underfunded compared with institutional care. For example, only 2% of health care spending in Canada is allocated to home-based care,[21] and only 2% of the elderly population receives such assistance.[1] Despite the reform rhetoric that increasingly calls for more community- and home-based care, community-based care may in fact not save government a substantial amount of money.[22–24]

Obtaining a clear definition and resolution of this issue in Canada is difficult because of the lack of solid,

Outcome

Institutional Care

Some fear of authority if complain (retribution). "Families tell us, 'If they complain, their resident will be punished.'" "A family that proves a strong advocate may then become labeled. They do become labeled." "Residents don't speak with government officers because facilities can narrow down the troublemakers. So, to be able to speak openly,... tends to be hard for residents." "People avoid complaining in case they could lose their place." "It's mostly been obstructionism and threats of retribution rather than actual retribution."

Separation of couples. "There isn't enough recognition, or hasn't been in the past, for rooms for both husband and wife. That's real sad for people." "They want to be together."

Placed in institution in another town. "Because of the lack of beds, people get relocated out of this community, or get relocated into this community, away from family and friends. This is because we have a shortage of beds. It can make it hard for a person facing institutionalization."

Community Care

Accommodation: changed expectations. "Not everything goes the way we want it to, but we feel fortunate to have community services because they are helpful." "Seven of 10 people in my club had a problem, but on the whole, they were so thankful to get the careworker to come, they didn't want to rock the boat." "It does seem to me that they might be a little worried that people might get cut off." "We were able to overcome our troubles. Is that because we're all adjustable?"

Coregivers suffer. "As the primary caregiver and a member of the family, there was no support for me. Many of us would love to care for our elderly, but there is no leave for caring for the elderly. I risked losing my career to care for my mother. And if you lose your career, you lose your pension. Then, when you need care, who's going to care for you? The pain is very deep that I had to institutionalize my mother, but I had no other choice."

Abuse: most obvious is financial abuse by family and 'friends.' "The other dynamic is family. If you talk with seniors, they are abused by some of the people around them. But, how are you going to turn your own kid in?" "The ones that have come to our attention are financial abuses more than any other kind." For example, a family wanted to sell their mother's home, against her wishes, for the money.

Figure 1. Examples of long-term care users' concerns are given here *(continued from page 339).*

statistical data on Canada's community-based care.[20] Government is curtailing expensive hospital and physician services. (An urban hospital has been closed in British Columbia. Attempts are ongoing to decrease the provision of some costly procedures. Hence, although less money is being spent, it is not being redistributed within the system.) It may be that savings to the federal and provincial governments occur primarily through cost shifts to localities.[25] Several years ago, many mentally ill patients were released from institutions. Unfortunately, appropriate replacement support in the community was never established. There is fear that the long-term care system may witness the same fate.[25] Thus, the jury is still out as to whether community-based care can achieve the posited objectives.

Health care reform will unquestionably place greater demands on community-based care. Informal caregivers are likely to bear the brunt of providing care in this event. Unpaid (informal) caregivers currently constitute the first line of care for elderly persons, providing as much as 80% of personal care for seniors.[25] Most (94%) of elderly persons who receive assistance obtain it through informal networks.[26] Government wants to expand community-based care. Perhaps the proposed reforms are at least partly grounded on the idea that informal caregivers can and will pick up the slack when institutional care and funding are curtailed. It must be asked whether this shift is feasible, efficient, and just.

Policy has recently begun to recognize the crucial role of informal caregivers. More services have been developed for their support. Among such support services are respite care, adult day-care centers, and caregiver support groups. The use of these services remains low, however.[27] Informal caregivers often wait until very late before accessing these services. In many instances, they wait until the elderly person needs facility care.[25]

Several participants in our focus groups and interviews mentioned that tax credits might go a long way toward bolstering their efforts to remain at home. None, however, referred to the recent additions to the medical expense tax credit. Perhaps this is because they, like the vast majority of elderly persons, rely heavily on informal care provided by relatives.

Expanding the services available to informal caregivers is not likely to reduce their willingness to provide care. These caregivers are determined to care for their elders themselves, a message repeated consistently throughout our focus groups. Clearly, the expansion of essential support services and encouragement toward their use would only strengthen this tremendous resource. Most caregivers of the elderly are themselves elderly or on the older side of middle-age. Most receive no help from the public sector. One of the most common scenarios is that of an elderly woman caring for her elderly husband. The physical, mental, and emotional drain of caring for someone, especially someone suffering physical and mental deterioration, is often overwhelming. Caregivers, especially those who are themselves elderly, often place their own health in jeopardy. Thus, instead of one person requiring long-term care services, the system may end up with two people in such need.[25]

In some instances, admission to an institution is both necessary and more desirable than home- or community-based care. It is likely, however, that institutions will receive smaller fractions of the resources directed toward long-term care. At the same time, these institutions will be confronted with older clients who are both physically and mentally frailer.[25] Could these patients, or some of them, be returned to communities that may not be properly equipped to care for them? The future of long-term care institutions in a reformed system is uncertain. Yet, the implications will be far-reaching.

Policy Implications

In exploring policy options to meet the demands for increased long-term care anticipated by the demographic imperative of an aging population, US policy makers have searched worldwide for ideas and models toward improving the fragmented maze of services that characterize long-term care in the United States. The Canadian long-term care system, and especially that in British Columbia, has been viewed as providing a road map to a rational system of access for service regulated by government as the principal payer, yet delivered by many private, nonprofit providers in a virtually complaint-free system. This has been accomplished through culturally determined modes of accommodation and negotiation.

In the United States, much of the policy emphasis is on outcomes research and has been focused on acute care and improvements in health status. Patient satisfaction is a key factor in high-quality outcomes of care.[16,28] Our findings, as well as those of others,[10,11,29] indicate that users are more concerned with issues relating to structure and process, such as privacy, autonomy, and choice. These have been widely measured dimensions in acute care, although professionals have not reached consensus on how and to what degree patient satisfaction contributes to quality of care. Within the United States, with the current era of market-driven reforms and the growth of for-profit managed care plans, interest in patient satisfaction has taken on greater importance as competition has increased for the market share of insured lives.

In light of the rapidly growing elderly population and despite the recognition of its implicit importance, systematic study of users' satisfaction with long-term care has not been given much attention. Users' satisfaction as an outcome of care and indicator of quality takes on added importance when dealing with vulnerable populations receiving long-term care. In such cases, the most appropriate outcome may be related to quality of life, as indicated by user satisfaction, because cure or a return to independent function is not a realistic expectation.[14] The connection between the structure and process of long-term care to users' satisfaction seems direct.

Conclusion

Our inquiry confirms that the Canadian system appears formally to be essentially complaint-free, but that users do experience dissatisfaction. They are concerned about structure and process matters, such as shortages of appropriate personnel in residential-, home-, and community-based services and with the nature and amount of services provided. At issue is the goal of providing care that can add to the quality of life of disabled persons in a rapidly aging population. Comparable qualitative research in the United States may serve to anticipate areas of users' concern. Once identified, it may be possible to increase the congruence of users' expectations with the capacity of the system to deliver.

Canada is currently undergoing the most dramatic reforms of its health care system since 1957, when the national health insurance system was established.[25] Long-term care, as with all other health care services, is being reformed in all Canadian provinces. British Columbia's long-term care system is receiving more attention than it has since the late 1970s when the current system was instituted. British Columbia may be able to rely on its already established long-term care infrastructure and administrative system with features such as case management and a single point of entry. Case management offers the opportunity to target clients who could maximize the health and economic benefits of community-based care. Such targeting is crucial for achieving optimal cost-effectiveness from community-based care by matching clients with appropriate services and weeding out clients who do not need such services.[1,3,20] Combined with other features, case management and a single point of entry could give British Columbia an advantage in reform efforts.

The challenge for now is to strengthen an already effective and efficient system. Regionalization could make the system more responsive to local needs. Reform provides an opportunity to address inequities and to shift the role of long-term care from monitoring disease to restoring functional capacity and social participation.[30]

Taking elderly persons out of institutions and returning them to their communities could further these goals. Assuming sufficient support, reform could make a good thing even better. But reform could pose the threat that expenditures will be curtailed but that consequent savings may not be redistributed within the long-term care system. Federal and provincial governments could cut their own costs by passing fiscal responsibility onto the localities as decision-making authority is devolved.

Reform could also pose a threat to community-based care physicians. They may be asked to provide more care for more people with more problems without notable increases in resources and funding. Informal caregivers may have to take on responsibility for even more care than they currently provide, perhaps for seniors who are physically and mentally even frailer.

The official reform rhetoric proposes to bring health care in "new directions" that are "closer to home" as health care moves "toward a better age." Accompanied with sufficient funding, resources, and attention, reform may well prove beneficial to users and all others concerned with and about long-term care. The future is uncertain, however. Pending more experience with the changing system, the question remains: Will reform bring long-term care "closer to home," or will the disabled elderly be left "home alone"?

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Epitomes

Important Advances in Clinical Medicine

Allergy and Immunology

Alan Goldsobel, MD, and Sheldon Spector, MD, Section Editors

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in allergy and immunology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in allergy and immunology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Allergy and Immunology of the California Medical Association, and the summaries were prepared under the direction of Drs Goldsobel and Spector and the Panel.

Recommendations for Immunizations in HIV-Infected Individuals

As the life expectancy of patients infected with human immunodeficiency virus (HIV) lengthens, health care professionals must give more consideration to prophylaxis against common diseases. Clearly, everyone should receive immunizations that are safe, effective, and clinically relevant, but not all pathogens are unusually virulent or overrepresented in HIV-infected individuals, and a vaccine's safety in this population can be difficult to determine. Live viral vaccines are usually contraindicated in immunosuppressed patients; in addition, the process of immunizing a patient theoretically could promote the activation of latent or controlled HIV infection. Since many HIV-infected patients are immunocompromised and may not mount an appropriate antibody response later in the course of HIV infection, it is important to consider administering vaccines soon after HIV infection when $CD4^+$ T lymphocyte counts are high and patients are clinically well.

An annual influenza vaccine is recommended for HIV-infected individuals, although patients with advanced disease are unlikely to mount an appropriate antibody response. There is no evidence that influenza is more common or severe in HIV-infected persons, but the vaccine is generally safe and well-tolerated. Hemophilus influenza type B is a problem in HIV-infected children, and the Hib vaccine is therefore recommended for them (and for all children). Since most flu in adults is not type B, its importance in older individuals is less clear, although HIV-infected adults lacking splenic function should receive the Hib vaccine. The vaccine against pneumococcal infection, a malady greatly increased in HIV-infected patients, is recommended, and revaccination is advised every 6 years. Adverse effects are rare.

The classic primary immunizations of childhood include those against measles, mumps, and rubella. Because these are live, attenuated viral vaccines, their use in symptomatic HIV-infected patients is a potential problem. Asymptomatic, immunologically naive, HIV-infected persons, however, would probably benefit from this vaccination during a measles outbreak. Oral polio vaccine is a live viral vaccine contraindicated in HIV infection, but the inactive form of the vaccine can be administered safely. Tetanus and diphtheria boosters, recommended every 10 years, appear to be safe in HIV infection.

Many HIV-infected persons have been exposed to hepatitis B. Unfortunately, the hepatitis B vaccine has shown a poor response rate in this group. Nonetheless, asymptomatic HIV-infected patients without evidence of antibodies to hepatitis B should receive the three-vaccination series. Interestingly, hepatitis A vaccine is more immunogenic in HIV-infected patients than most other vaccines. Travelers to areas endemic for hepatitis A who have no immunity should be vaccinated with this killed, inactivated viral vaccine.

The recommendations for vaccinations for foreign travel change frequently depending on epidemics, sanitation conditions, and other factors. The live, attenuated yellow fever vaccine is contraindicated, but many of the inactivated vaccines may be safe for use in HIV-infected individuals. In general, a careful evaluation of the potential risks and benefits of a given vaccine is always the first step in developing a individual immunization regimen.

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Drug Reactions in HIV/AIDS

Adverse reactions to drugs are frequent in patients with human immunodeficiency virus (HIV) infection and AIDS. The most commonly prescribed drug for AIDS patients is trimethoprim-sulfamethoxazole (TMP-SMX); it is also the most common source of adverse reactions. Up to 40% of patients receiving high-dose TMP-SMX develop a maculopapular diffuse rash, often with fever and malaise. Similar reactions have been reported with clindamycin, diapsone, pyrimethamine/sulfadoxine, aminopenicillins, clavulanate, thalidomide, atovaquone, nevirapine, delavirdine, rifampin, probenecid, and 1592 (a new antiviral drug).

The cause of these reactions is not clear. Immunologic processes might be involved, since patients with HIV and AIDS demonstrate immunoactivation as well as immunodeficiency. A polyclonal increase of immunoglobulins (including IgE), increased circulating immune complexes, and an increased number of activated $CD8^+$ cells may be secondary to various infections. Abnormal hepatic metabolism may result in the persistence of drug metabolites that act as antigens or have direct cellular toxicity. Alternatively, an incompetent immune system may fail to clear the metabolites. Finally, incidence of certain viral infections, such as herpes simplex virus, hepatitis B virus, cytomegalovirus, and Epstein-Barr virus (EBV), is increased in patients with HIV and AIDS. These infections may stimulate the immune system, predisposing the patients to drug reactions such as that between EBV and aminopenicillins. There is no conclusive evidence that the incidence of IgE-mediated reactions to drugs, such as penicillin-induced anaphylaxis, is increased in patients with HIV/AIDS. Rather, the incidence of some adverse drug reactions seems to increase with advancing immunodeficiency. A possible participation of hepatic drug metabolism may explain the success of incremental dosing (as with nevirapine and delavirdine) and desensitization protocols in minimizing the problems.

The most common clinical presentation of an adverse drug reaction in patients with HIV/AIDS is rash. The rash, which starts 7 to 12 days after initial exposure to the culprit agent, is usually diffuse, erythematous, maculopapular, and pruritic and is frequently accompanied by fever and malaise. Conjunctivitis is common, but mucous membrane involvement is not. Susceptible patients may have identical or nearly identical symptoms from several agents. More severe reactions, such as Stevens-Johnson syndrome, bullous lesions, and toxic epidermal necrolysis, also may occur. Hepatic and hematologic abnormalities can stem from immune-mediated injury or direct toxicity; rare cases have been reported of eosinophilic pneumonia possibly secondary to drugs.

The diagnosis of adverse drug reactions rests mainly on a good history, especially a detailed drug history, timing of introduction of the suspected agent, and clinical symptoms and physical examination.

Withdrawal of the offending agent is usually successful in treating the reactions. Although severe bullous rashes are often treated with corticosteroids, the effects of this treatment are difficult to assess. We have noted remarkable responses to intravenous immunoglobulin infusion in a few seriously ill patients with bullous skin rashes.

Although avoiding the offending agent is the safest method to treat the problem, it may not be the best approach if the agent is the drug of choice and there is no tolerated alternative. In such circumstances, a careful desensitization may be attempted. Desensitization has been successful with TMP/SMX, clindamycin, sulfadiazine, and other agents, but probably should not be attempted for such serious or life-threatening reactions as anaphylaxis, bullous dermatitis, or renal or hepatic failure.

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Latex Allergy—The Latest Insights

Urticaria to latex has been reported as early as 1927 and more recently in 1979. Fatal reactions to latex-tipped barium enema catheters brought attention to the potentially serious nature of the allergy around 1990. In recent years, awareness of the condition has risen, as has exposure to latex: more than 40,000 products contain latex, and latex gloves are omnipresent in health care settings. As a result, more and more latex-sensitive patients are being identified. Groups reported to have high prevalence rates of latex allergy include health care workers, dental workers, rubber industry workers, housekeepers, spina bifida patients, and patients undergoing frequent catheterizations or multiple surgeries.

Two potential mechanisms for sensitization are common: direct contact and inhalation of aerosol latex proteins carried on the cornstarch of powdered gloves. Latex-sensitive individuals experience symptoms that vary from localized hand symptoms such as itching or urticaria to a wide range of systemic reactions including

generalized urticaria, sneezing, tearing, coughing, wheezing, and even anaphylaxis with hypotension shortly after exposure to latex products. Some investigators have noted a progression of symptoms in health care workers from contact dermatitis to localized urticaria to systemic IgE-related symptoms. On the other hand, a significant number of patients who develop systemic IgE symptoms do so without any preexisting contact dermatitis.

In a patient known to have other allergies, it can be difficult to determine whether latex exposure is precipitating symptoms or simply aggravating them. In questionnaires, many people self-report symptoms that could be from latex exposure, but few cases are confirmed by diagnostic tests. Recent epidemiologic studies have reported prevalence rates in health care workers ranging from 2.9 to 17%, but ascertainment bias may be a factor in those results. Better-designed epidemiologic studies as well as longitudinal studies must be undertaken.

The immunologic mechanism for systemic reactions to latex is a type I hypersensitivity mediated by IgE antibodies directed against latex rubber proteins. According to one study, 57 of the 200 proteins in latex bind to human IgE. Seven sensitizing latex proteins have been identified, cloned or partially characterized, and assigned allergen designations of Hev b1–b7 by the International Union of Immunological Societies. A high percentage of patients who are latex sensitive are also positive for at least one food skin test, suggesting epitopes common to both latex and food allergens. Foods that cause allergic reactions in latex-sensitive patients include banana, avocado, kiwi, chestnut, potato, cherry, apricot, papaya, passion fruit, and melon.

Three FDA-approved latex-specific IgE in vitro tests are available: Alastat, CAP, and Hycor. Although these assays claim high sensitivity and specificity, their accuracy and reliability can only be determined with broader clinical experience in various populations. A challenge procedure may be used to clarify the diagnosis in patients who have clinical histories that conflict with skin test or in vitro test results, and developing standardized challenge procedures is an important area of research. There is no standardized skin test reagent—testing patients with extracts of unknown potency has resulted in systemic reactions, limiting the use of skin testing. A multicenter clinical trial using a Food and Drug Administration–approved non-ammoniated latex extract is underway.

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Antileukotrienes—1997 and Beyond

Antileukotrienes represent a new class of asthma medication. They modulate inflammation, they have a mild bronchodilator activity, and their virtual lack of side effects represents an advantage over many other antiasthmatic compounds. Antileukotrienes have the ability to counter most of the basic pathogenic mechanisms of asthma, and they modify increased vascular permeability and edema formation, increased mucus production, bronchoconstriction, and cellular inflammatory exudate.

Two main classes of agents modulate leukotrienes, the leukotriene receptor antagonists and the inhibitors of key enzymes involved in the synthesis of leukotrienes. The latter class can be divided into two further groups: those that inhibit 5-lipoxygenase [5-LO] and those that inhibit the activity of 5-lipoxygenase activating protein (FLAP). Of the many compounds currently under study, only two agents, zafirlukast and zileuton, have received approval from the Food and Drug Administration (FDA).

The potential usefulness of the antileukotrienes has been demonstrated in various experimental and clinical studies. Their mechanisms vary, suggesting that agents within the leukotriene category should be substituted if clinical response is not adequate. For example, virtually all the receptor agonists improve dose response, and some agents, such as zafirlukast and the FLAP inhibitor BAY 10005, block both early- and late-phase allergen challenges.

Many agents block hyperresponsiveness as measured by methacholine or histamine inhalation challenge. They include the receptor antagonists zafirlukast and pranlukast and the synthesis inhibitors BAY 10005 and MK-886. Almost all of the leukotriene antagonists and inhibitors have been shown to block exercise-induced asthma and cold air challenge to some degree.

It is thought that antileukotrienes might be particularly effective in the subgroup of patients with aspirin idiosyncrasy. The leukotriene antagonist SKF-104353 was shown to be an effective blocker in five subjects studied; similarly, pranlukast in a single dose of 225 mg showed an impressive effect in six aspirin-sensitive patients. A single dose of 750 mg of montelukast blocked an inhaled lysine aspirin challenge in patients with aspirin sensitivity, and zileuton in a dose of 600 mg four times a day for 6 to 8 days also was found to attenuate aspirin challenges and decrease urinary LTE_4 levels. In the latter study, the agent was also found to attenuate nasal, gastrointestinal, and dermal responses to aspirin.

Many researchers have studied antileukotrienes in clinical asthma. For example, compared with baseline measurements, patients receiving 40 mg of zafirlukast experienced a 46% decrease in nighttime awakening, a 30% decrease in albuterol use, and a 26% improvement in daytime symptoms. The oral compound MK-571 has also been found to improve asthma symptoms and pulmonary function and decrease beta-agonist use. Verlukast has shown similar effects, as have montelukast, pranlukast, and zileuton.

In general, the antileukotriene agents are very safe. Earlier agents that caused significant elevations of liver function tests are no longer manufactured, but some concerns regarding liver function remain. Zileuton ingestion has been associated with mild and transient elevation of liver enzymes that generally reverts to normal with continued therapy or cessation. The FDA has suggested that monitoring be done monthly for the first few months, and periodically thereafter. Churg-Strauss syndrome has been found in association with zafirlukast when corticosteroid anti-inflammatory therapy was being tapered. Thus asthma patients in whom corticosteroid therapy is being reduced should be carefully monitored. Adrenal suppression and cataracts have been mentioned as potential side effects; further study is required.

Antileukotrienes are currently recommended for mild persistent asthma by the National Heart, Lung and Blood Institute, and they may be effective in other subgroups of asthma.

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Combination Therapy for HIV Disease

As a result of recent advances, the treatment of HIV disease is now firmly based on HIV immunopathogenesis and viral dynamics. This paradigm shift—along with new, potent anti-retroviral drugs, a better understanding of drug resistance, and the ability to monitor viral load—has engendered updated recommendations for anti-retroviral therapy.

The concept of virologic latency after primary HIV infection is no longer tenable. HIV immunopathogenesis reveals that viral replication and clearance, as well as $CD4^+$ cell destruction and replacement, are rapid, continuous, high-level processes at all stages of the disease. Estimates suggest that 10 billion virions and 2 billion $CD4^+$ cells are produced and destroyed each day, and that the plasma virus half-life is only 6 hours. More than 99 percent of plasma viremia results from these ongoing cycles of infection in $CD4^+$ lymphocytes. Eventually, the immune system is overwhelmed by the unrelenting assault.

HIV infects multiple cellular compartments. Actively productive $CD4^+$ cells with short half-lives make up the first compartment, the major reservoir of virus in the body. A second compartment of longer-lived tissue macrophages and follicular dendritic cells accounts for 1% of the viral burden. A third compartment of chronically infected cells may exist (perhaps in the brain and cerebral spinal fluid), offering proviral DNA a long-term, possibly life-long, sanctuary site. The mathematical model for eradication of HIV suggests that complete viral suppression for a period of 2 to 3 years may eradicate the virus from the host in the first two compartments, but a risk of relapse remains from the sanctuary sites.

The ability to quantitate the level of HIV-1 RNA in the plasma (viral load) has been essential to our increased understanding of viral pathogenesis and anti-retroviral efficacy. Viral load is a practical and reliable marker of disease progression and treatment benefit.

Recent data has demonstrated a strong relationship between viral load and clinical outcomes. Natural history studies have demonstrated that baseline viral loads predict over a 10-year period of observation the rate of $CD4^+$ T-lymphocyte decline, the time to AIDS, and the time to death from AIDS. Similarly, clinical trials of nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and protease inhibitors have consistently shown a strong correlation between reductions in viral load and reduced risk of $CD4^+$ T-cell decline, AIDS, or death from AIDS.

Within the past year, five new drugs have been approved for the treatment of HIV-1 infection: two nonnucleoside reverse transcriptase inhibitors (nevirapine and delavardine) and three protease inhibitors (ritonavir, indinavir, and nelfinavir). The addition of these agents has resulted in a growing number of potent virus-suppressing combination regimens. The term "highly active anti-retroviral therapy" (HAART) has been coined to describe these new, very effective, combinations.

The promise of these new combinations notwithstanding, it has become clear that the development of drug resistance remains the Achilles heel of anti-retroviral therapy. A new generation of HIV is produced in 2.6 days, yielding 140 generations per year. Assuming 10 billion replicative cycles per day, every possible mutation in the HIV genome can occur several times a day. Consequently, if HIV replication is not completely arrested, mutants will rapidly arise. Genotypic and phenotypic laboratory assays for drug resistance are in development.

Potent anti-retroviral combination regimens initiated in moderately advanced disease have demonstrated impressive immunologic, virologic, and clinical responses. The immunologic response is incomplete, however, with respect to full restoration of $CD4^+$ cell number and function, thus arguing in favor of earlier intervention.

The mantra of HIV therapy has become "hit early, hit hard." Significant scientific rationale exists for the new, more aggressive goal of suppressing HIV replication as completely as possible throughout the entire course of infection. Powerful, theoretical rationale exists as well for intervening as early as possible in the course of HIV disease to avoid irreversible immune deficits. Highly

effective combination anti-retroviral therapy is the new standard of care.

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Advances in Allergic Rhinitis Pharmacotherapy

A recent survey shows the prevalence of allergic rhinitis to be at least 14% in the US population. Therapeutic options for allergic rhinitis are threefold: pharmacotherapy, immunotherapy, and environmental control. Pharmacotherapy has provided the major advances over the last 10 years with regard to improved efficacy and safety in the treatment of this disease.

Five agents are now available in the category of oral second-generation antihistamines: terfenadine, astemizole, loratadine, cetirizine, and fexofenadine. These histamine receptor antagonists are less sedating than their first-generation predecessors, and thus are well tolerated by patients. Terfenadine and astemizole, however, can cause QT prolongation and, in rare cases, a serious and potentially fatal cardiac arrhythmia. The Food and Drug Administration has therefore recommended removal of terfenadine from the market. The other three agents do not appear to have this property. Advantages of the second-generation antihistamines include a complete lack of somnolence and mental impairment (astemizole, loratadine, fexofenadine), the convenience of once-a-day (astemizole, loratadine, cetirizine) or twice-a-day (terfenadine, fexofenadine) dosing, and, consequently, improved patient acceptance and compliance. Liquid preparations and pediatric indications (age 6 years and up) now exist for loratadine and cetirizine. Certain antihistamine-decongestant combination agents are on the market, although patients who use them need to be warned about potential stimulatory side effects from the decongestant. Second-generation antihistamines have also recently become available for topical use. Azelastine hydrochloride, a moderately effective intranasal spray, is particularly useful in decreasing nasal itching; mild sedation occasionally occurs due to its systemic absorption via the nasal mucosa.

The well-proven potency, efficacy, and safety of intranasal corticosteroids have made them the drugs of choice for any patient with frequent, chronic, or severe symptoms of allergic rhinitis. A number of topical agents are available (beclomethasone diproprionate, budesonide, flunisolide, fluticasone, triamcinolone, dexamethasone). Comparison studies evaluating topical steroids versus oral antihistamines repeatedly show intranasal corticosteroids to be superior. Unlike all other pharmacotherapy agents, when used alone, intranasal corticosteroids can improve all four of the major symptoms of allergic rhinitis (itch, rhinorrhea, sneeze, and congestion). Their use has increased for a variety of reasons, including a better understanding of the inflammatory nature of allergic rhinitis and the decision to introduce them earlier and maintain them longer when allergen exposure or symptoms continue. They are available as either a wet aqueous spray or a dry aerosol spray, making them convenient and well accepted by most patients. Differences in clinical efficacy between agents is minimal, so selection of a specific nasal steroid usually depends on cost, formulary availability, and patient preference (aqueous or aerosol). At recommended doses, intranasal corticosteroids are free of significant adverse effects.

Another topically active anti-inflammatory agent, cromolyn, has been found to be so safe after years of use that it was recently made available without a prescription. Cromolyn is an nonsteroidal nasal spray whose mode of action is primarily preventive via mast cell stabilization and, overall, less effective than nasal corticosteroids.

Oral anticholinergic therapy has been tried for years as therapy for allergic rhinitis, but adverse effects (such as dry mouth and eyes) have limited its use. A topical anticholinergic medication has recently become available that circumvents the side effects of the oral form: ipratroprium bromide. This nasal spray, available in two strengths (0.03 and 0.06%), appears to be an effective adjunct in controlling rhinorrhea.

New agents and approaches hold additional promise for the treatment of allergic rhinitis. The leukotriene receptor and pathway antagonists, available for asthma, are being tested as therapeutic agents in oral and topical forms. Monoclonal antibodies to IgE and to cytokines important in allergic inflammation are still in early experimental stages but will likely be tried as therapy for this disease.

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Treatment of Chronic Urticaria

Chronic urticaria is a disease of unknown origin. In a study of chronic urticaria patients, a 5-day diet of rice, lamb, and water had no effect on the majority of symptoms; thus its manifestations were not due to an exogenous foodstuff or food additive. The theory that chronic urticaria is, rather, an autoimmune disorder holds in at least 40% of patients. These patients have an IgG antibody directed to the α subunit of the IgE receptor on cutaneous mast cells. Mast cell degranulation may lead to a late phase-like cutaneous reaction that causes the infiltrative hive characteristic of chronic urticaria. This infiltrate consists of a perivascular collection of $CD4^+$ T lymphocytes, a surprisingly large number of monocytes, perivascular mast cells, and variable numbers of eosinophils with eosinophil-derived cationic proteins identifiable in about 65% of subjects even if intact eosinophils are not evident.

In an additional 50 to 60% of patients, IgG anti $Fc_{\varepsilon}RI\alpha$ antibody is not demonstrable functionally (histamine release) or by binding (immunoblot directed to α). The cause of their condition remains an enigma. In addition, some patients' sera cause histamine release but do not bind to the α subunit, suggesting an alternative mast cell degranulating substance in their sera. It is curious, and so far unexplained, that these autoantibodies, when present, lead only to cutaneous disease rather than rhinitis or asthma.

The aforementioned observations support treatments other than high-dose antihistamines for treating chronic urticaria. For example, a gradually tapering alternate-day steroid protocol may be effective for severe disease. The rationale for steroid administration is no different from its rationale in allergic rhinitis or asthma, but in this case, systemic rather than topical administration is required. Experimental approaches to treating chronic urticaria include plasmapheresis and administration of intravenous gamma globulin or cyclosporine, but further studies are needed.

Steroids cannot directly inhibit cutaneous mast cell degranulation, emphasizing the importance of the cellular infiltrate in the pathogenesis of chronic urticaria. In contrast, most physically induced hives (cold urticaria or dermatographism, for example) are generally unresponsive to corticosteroids but respond to antihistamines because they have no associated late phase response and the symptoms are due solely to mast cell degranulation.

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Inhaled Corticosteroids for Asthma Therapy

Inhaled corticosteroids, which suppress both the inflammatory process and the bronchial hyperreactivity that are characteristic of asthma, have become the first-line therapy for long-term control of chronic asthma. Because inhaled corticosteroids are delivered in very small doses directly to the airways, they cause far fewer side effects than larger doses of corticosteroids delivered systemically. Accordingly, there is a growing trend toward using these agents in even the mildest cases of asthma. In fact, a recent report demonstrated a decreased risk of hospitalization for asthma with the use of inhaled corticosteroids.

The inhaled corticosteroids currently available in the US for treating asthma include beclomethasone dipropionate (BDP), budesonide (BUD), triamcinolone acetonide (TAA), flunisolide (FL), and fluticasone propionate (FP). Few comparative trials have examined the different products; there is a need for more studies.

The ideal inhaled corticosteroid should have low systemic bioavailability, high topical potency, and rapid clearance of the portion that reaches the systemic circulation. Only 10 to 15% of the inhaled dose of corticosteroid reaches the lungs, and the balance is deposited in the posterior pharynx and oral cavity or is ingested. The portion of the absorbed drug not neutralized by a first pass through the liver enters the systemic circulation. Safety is paramount because these drugs are used over a long period of time and frequently in children. While it is sometimes assumed that all inhaled corticosteroids have essentially equivalent efficacy, differences in safety profiles do exist.

BDP is the most widely studied inhaled corticosteroid. It has efficacy similar to a TAA dose, which delivers twice the micrograms per inhalation. BDP is metabolized to its active form in the lung. Its active metabolite has a greater affinity for corticosteroid receptors than BUD but is equivalent in its therapeutic efficacy and safety profiles. On the other hand, 1000 mg of BUD (in dry powder form) achieves lung deposition approximately twice that of 1000 mg delivered by metered dose inhaler (MDI), suggesting a greater bioavailability with the dry powder form. Systemic bioavailability of BUD and FP is determined principally by their bioavailability in the lung.

BDP and BMP have the shortest half-lives—30 and 37 minutes, respectively. The elimination half-life for BUD is estimated to be 2.3 hours, whereas the elimination half-life of FP is 7.8 hours, the longest of all the inhaled steroids. The systemic bioavailability of FP from the lungs is 30% of the drug delivered from the actuator. FP therefore produces a roughly three-fold increase in the likelihood of systemic side effects because of its prolonged half-life and greater absorption from the lungs.

The potential for systemic side effects, such as hypothalamic pituitary-adrenal axis suppression, cataracts,

and growth retardation, rises with increasing doses of inhaled corticosteroids. Therefore, the need for high doses of inhaled corticosteroids in a patient should be constantly reassessed so as to administer the lowest effective dose. In one study, when the same microgram doses of BDP, TAA, and FL were administered, equivalent suppression of 24-hour urinary-free cortisol excretion was observed. FP had greater adrenal suppression than BUD, however, at equivalent microgram doses even when accompanied by a mouth-washing procedure to prevent oral bioavailability.

Overall, selected inhaled corticosteroids (such as BDP) have been associated with remarkably few side effects at doses up to 400 µg per day in children and up to 800 µg per day in adults. Even at higher doses—up to 2000 µg per day—relatively few adverse events have been reported. In conclusion, the small risk associated with inhaled corticosteroids must be balanced against the far greater dangers of failing to control chronic asthma.

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Intravenous Immune Globulin in Neuromuscular Disorders

Intravenous immune globulin (IVIG) is a polyvalent immunoglobulin that contains more than 90% monomeric IgG with small amounts of other immunoglobulins, such as IgA, IgM, and possibly IgE. It is prepared from plasma derived from a large pool of volunteer donors. (The donors are well screened for human immunodeficiency virus [HIV], human T-cell lymphotropic virus, and the hepatitis A, B, and C viruses. In addition, HIV and hepatitis B virus are inactivated by a fractionation process, and the plasma is treated with solvents, detergents, or enzymes and incubated at low pH to inactivate hepatitis C and other viruses.)

IVIG is primarily used as a replacement therapy for patients with antibody deficiencies. The successful use of high doses of IVIG to treat children with idiopathic thrombocytopenic purpura led to high doses (approximately a total initial dose of 2 g/kg body weight over five consecutive days) being used in a large number of autoimmune disorders, including several neuromuscular disorders. In some, such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, and dermatomyositis, the results of controlled clinical trials have demonstrated definite beneficial effects. In fact, a number of controlled studies, including multinational and multicenter studies, of Guillain-Barré syndrome—a monophasic acute demyelinating polyneuropathy characterized by severe weakness or paralysis of limbs and respiratory muscles—have demonstrated that high-dose IVIG therapy is at least as effective as plasmapheresis or combination of IVIG and plasmapheresis. The efficacy of IVIG in other disorders is either anecdotal or not fully substantiated by controlled studies. The beneficial effect of the combination of intravenous methylprednisone plus IVIG over IVIG alone remains to be determined.

Taking into consideration cost, safety, convenience, and practicality, IVIG is preferred for small children or patients with poor venous access, patients with severe autonomic dysfunction or compromised hemodynamics, and patients in hospitals in which plasmapheresis is either not available or not routinely performed.

Unlike Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), characterized by the slow onset of weakness, areflexia, and impaired sensation, requires long-term therapy to maintain improvement. The treatments for CIDP are steroids, high-dose IVIG, and plasmapheresis. The response to steroids is sometimes slow, and prolonged therapy increases the risk for severe side effects. Controlled and randomized studies have demonstrated that high-dose IVIG and plasmapheresis are equally effective in improving muscle strength, neuropathic symptoms, and amplitude of evoked muscle-action potentials. At this stage, it is unclear what dose should be used for maintenance therapy, although a monthly administration of 1 g/kg body weight has been recommended.

Multifocal motor neuropathy (MFMN) is a disorder of slow onset of weakness and muscular atrophy with areflexia and without sensory loss. It is characterized by conduction block of the motor axons and by the presence of GM1 ganglioside antibodies. IVIG is the treatment of choice for MFMN. IVIG therapy is associated with diminution of symptoms and resolution of electrophysiological conduction block, although GM1 antibody titers may be unaffected. If the efficacy of IVIG therapy diminishes after several months of treatment, the coadministration of intravenous cyclophosphamide may be indicated.

Dermatomyositis is a myopathy characterized by weakness of proximal muscles, violaceous rash on the face and extremities, and deposits of immune complexes in the capillaries. Double-blind and controlled studies have demonstrated that high-dose IVIG induces clinical improvement that is associated with inhibition of the deposition of components of complement activation and downregulation of intercellular adhesion molecule-1 and major histocompatibility complex (MHC) class I. Since steroids are the treatment of choice, IVIG is indicated for steroid-resistant patients or for patients in whom steroids are contraindicated.

The side effects of IVIG treatment occur in less than 10% of cases, and are usually minor: mild-to-moderate headache, chills, myalgia, chest discomfort, fever,

fatigue, and nausea. Most of the side effects can be prevented or treated by administration of nonsteroidal anti-inflammatory agents and by slowing the rate of IVIG infusion. Aseptic meningitis occurs in 10% of cases, responds to strong analgesia, and subsides in 24 to 48 hours. Other rare adverse reactions include skin rash, anaphylaxis, and renal tubular necrosis.

The mechanisms by which IVIG exerts its beneficial effects in neuromuscular disorders are not clearly understood, but various immunomodulatory effects have been proposed. IVIG contains a variety of anti-idiotypic antibodies that bind to and neutralize pathogenic autoantibodies, thus preventing their interaction with self-antigens. Along with IgG, molecules in IVIG that have immunomodulatory effects in neuromuscular disorders include antibodies to various cytokines and T cell receptors and soluble CD4, CD8, and MHC class II antigens.

Determination of the optimal dose, frequency, duration, and the mechanisms of action of IVIG in various neuromuscular disorders will continue to challenge scientists. Meanwhile, because IVIG is expensive, the clinician should be judicious in the use of IVIG as a therapeutic agent in neuromuscular disorders.

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Alerts, Notices, and Case Reports

Paralytic Shellfish Poisoning in Kodiak, Alaska

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PARALYTIC SHELLFISH POISONING (PSP) occurs worldwide and its incidence may be increasing.[1] In North America PSP has been reported mainly in Canada, the Pacific Northwest, California, and New England. Paralytic shellfish poisoning is caused by ingestion of shellfish containing one or more of several saxitoxin analogs.[2] Saxitoxins act by blocking sodium ion movement through voltage-gated sodium channels on excitable cell membranes.[2] Generally, PSP results in mild symptoms such as paresthesias, including perioral and extremity numbness and tingling, and gastrointestinal symptoms, including nausea and vomiting.[3,4] More severe cases may result in neurologic symptoms such as dysarthria, dysphagia, ataxia, diplopia, weakness, and a dissociative feeling. Death is unusual and generally results from respiratory paralysis. In severe cases, progression from onset of symptoms to respiratory arrest may be rapid. The case reported here occurred as part of a larger outbreak that has recently been described in full.[5]

Report of a Case

This 28-year-old man presented to the hospital on May 24, 1994, with gastrointestinal and neurologic symptoms.

The patient had been in good health until 4 hours previously when he experienced the acute onset of perioral paresthesias, nausea, and vomiting. He subsequently suffered progressive severe headache, dysarthria, dysphagia, and ataxia and presented to a local hospital. During triage evaluation, the patient was anxious and had pink skin and mucous membranes. His blood pressure was 172/110 mmHg, his pulse 83, and his oxygen saturation 97%. Fifteen minutes later he became apneic and cyanotic while his oxygen saturation decreased sharply to 55%. After a brief period of bag and mask ventilation, he was intubated with an endotracheal tube and mechanically ventilated.

The patient was a recent immigrant from El Salvador who spoke little English and worked for a fish cannery. He had a past history of gastric bleeding 2 years previously but was taking no medications at the time of his current illness. One to two hours before illness onset, he had been drinking beer and collecting, roasting, and eating mussels from a beach on Kodiak Island. He had no recent history of trauma, fever, or upper respiratory symptoms.

On rapid physical examination following the onset of apnea, the patient was afebrile with a blood pressure of 244/131 mmHg and a pulse of 135. His head, neck, lymph nodes, lungs, heart, abdomen, and skin were normal. On neurologic examination, his pupils were sluggishly reactive and dilated and he was areflexic and unresponsive to vocal or pain stimuli.

The patient's complete blood count and serum levels of electrolytes, glucose, calcium, blood urea nitrogen, creatinine, and creatine kinase were normal; his serum lactic acid dehydrogenase was 196 U per liter (normal range 0–190 U/L). Toxicology screening was negative except for an ethyl alcohol level of 10 mg/dL. Testing for arterial blood gas levels performed after respiratory arrest and during bag and mask ventilation with 100% oxygen yielded a pH of 7.3, PaO_2 of 196 mmHg, a $PaCO_2$ of 28 mmHg, and a bicarbonate of 14 mEq/L. On chest radiographic examination he displayed left lower lobe atelectasis and an electrocardiograph demonstrated sinus tachycardia. Computerized tomography scans of the abdomen, chest, and head were unrevealing. Treatment consisted of supportive care and management of hypertension.

During neurologic examination 4 hours after respiratory arrest, the patient did not respond to voice commands, his pupils were fixed and dilated, his fundoscopic examination was normal with clear disc margins, he displayed no facial grimace when a cotton swab was applied to his nasopharynx, showed no response to finger nail compression, his doll's eyes maneuver test was negative, and Babinski, cremasteric, abdominal, and deep tendon reflexes were absent. At this point the patient was not receiving sedative or paralytic medications. Consideration was given to performing tests to determine the possibility of brain death until a diagnosis of paralytic shellfish poisoning was taken into account.

Five hours after intubation, the patient moved his toes spontaneously; 30 minutes later he opened his eyes and breathed against the ventilator. He subsequently extubated himself and was reintubated after receiving vecuronium bromide and diazepam. Fifteen hours after his respiratory arrest, following a period of increasing

(Gessner BD, Middaugh JP, Doucette GJ. Paralytic shellfish poisoning in Kodiak, Alaska. West J Med 1997 Nov; 166:351–353)

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consciousness during which he continued to receive diazepam intermittently, his endotracheal tube was removed. Thirty-two hours after respiratory arrest, the patient was awake, oriented to person, place, and time, and complained only of weakness, although he could walk without assistance. He had no dysphagia, dysarthria, or diplopia. On examination, he had a diminished but present gag reflex, normal deep tendon and absent Babinski reflexes, and normal cranial nerve (II–XII) function.

The course of the patient's hypertension reached a peak 6 to 7 hours after presentation or 11 to 12 hours after eating mussels. This hypertension was refractory to two 1-mg intravenously administered doses of metaprolol and a 10-mg dose of nifedipine administered sublingually approximately 5 hours after presentation and a 10-mg dose of nifedipine administered 6 hours after presentation. Between 7 and 8 hours after presentation, and 2 to 3 hours after the gradual return of neurologic function, the patient's blood pressure began to decrease; 24 hours after presentation it measured 108/61 mmHg.

Subsequent testing of mussels from the implicated beach detected a PSP toxin concentration of 18,684 µg per 100 g of tissue; based on a body weight of 91 kg, the patient ate an estimated 411 µg toxin per kg body weight. An analysis of the PSP toxin components showed that the most prevalent compounds were gonyautoxin 2 (22.8 mole percent), gonyautoxin 1 (19.5 mole percent), C1 (16.1 mole percent), gonyautoxin 3 (14.2 mole percent), and C2 (12.0 mole percent).

Discussion

This case illustrates the dramatic onset, presentation, and recovery commonly associated with severe PSP and emphasizes how important it is that health care providers recognize the symptoms of this disease. The initial clinical presentation of PSP may resemble that associated with ingestion of other toxins found in seafood, including tetrodotoxin and ciguatoxin,[6,7] as well as poisoning by pesticides containing anticholinesterases.[8] In areas such as Alaska, botulism must also be included in the differential diagnosis. Severe PSP may present with, or rapidly progress to, respiratory arrest[3,4] and (as was seen in the case we present) a clinical picture resembling deep coma. Unless clinicians consider the possibility of PSP, an unnecessarily extensive diagnostic workup may be undertaken. More tragically, in areas where sophisticated mechanisms to determine brain death do not exist, health care providers may decide that further therapeutic intervention is futile and discontinue life support measures. Fortunately, the physicians caring for the patient presented here recognized that his symptoms might be consistent with PSP, despite a clinical picture that resembled deep coma.

Using an animal model, Benton et al demonstrated the reversal of cardiorespiratory arrest using an α-saxitoxin antibody;[9] other studies have suggested that ethyl alcohol ingestion may protect against the effects of PSP toxins.[4,10] Despite these findings, the clinical management of patients with PSP remains largely life supportive. Charcoal and gastric lavage may be attempted[8] regardless of a history of having vomited, because in at least one other report the authors describe a patient who had significant amounts of shellfish in her stomach at autopsy despite vomiting before death.[8] Respiratory support should be provided until the return of adequate respiratory function. When initiated before hypoxic damage, ventilator support may lead to rapid and complete recovery.[3,4] Clinicians should be aware that, although cardiac sodium channels are relatively resistant to saxitoxins, PSP toxins may act directly on cardiac tissue and at high concentrations may lead to significant cardiac effects, including cardiovascular failure.[5,11–13]

Few investigators have attempted to evaluate the effect of paralytic shellfish poison toxin on blood pressure, although one investigation in which blood pressure measurements were documented found hypertension.[10] Similarly, the patient described in the current report had evidence of systemic arterial hypertension at the time of presentation. Despite pharmacological intervention and his unconscious state, his hypertension did not resolve until after the return of neurologic function. The mechanism of PSP toxin–induced hypertension is not known, and therefore specific treatment recommendations cannot be made. The lack of response to nifedipine and metaprolol in our patient suggests that his hypertension was not the result of changes in calcium channel or β-adrenergic activity.

Most previous investigations of PSP outbreaks have not attempted to define the minimum lethal concentration of the toxin per body weight. One team of investigators has identified saxitoxin B1 as the principal toxin and estimated the lethal concentration to be 86 to 788 µg per kilogram of body weight.[3] We have found that with predominant shellfish toxin components of C1, C2, and the gonyautoxins, 411 µg per kilogram of body weight constitutes a lethal concentration in the absence of respiratory support.

Because recovery with respiratory support may be rapid and complete, health care providers should know the signs, symptoms, and appropriate management of PSP. In addition, they should report all suspected cases of PSP to local health authorities so that appropriate warnings may be issued and further cases prevented.

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Resolution of Propylthiouracil-Induced Hepatic Failure After Treatment of Thyrotoxicosis

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A RELATIONSHIP between thyroid diseases and the liver has been recognized for more than a century.[1] Hepatic dysfunction has been found in cases of long-standing hyperthyroidism, usually in association with congestive heart failure.[2,3] Elevated levels of serum transaminase, alkaline phosphatase (ALP), and bilirubin are frequently observed in thyroid storm. In rare cases, patients suffering from hyperthyroidism presented with signs and symptoms of liver disease, which disappeared after successful treatment of thyrotoxicosis.[4–8] With the introduction of effective treatments for hyperthyroidism, jaundice and hepatic dysfunction are now uncommon in patients with hyperthyroidism; however, hepatotoxicity from propylthiouracil (PTU) or methimazole remains a rare but well-established complication in these patients.[9] In most cases, liver function improves after antithyroid drugs are discontinued, although fatal cases of PTU-induced hepatic failure have been reported.[10–13] In the present report we describe a case of Graves' disease complicated by PTU-induced hepatic necrosis associated with persistent severe thyrotoxicosis. Hepatic failure resolved after treatment of thyrotoxicosis, suggesting that achievement of a euthyroid state may be of great benefit in such cases.

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Report of a Case

This 21-year-old woman was transferred to the medical facility at the University of California, San Francisco (UCSF) for continued treatment of Graves' disease and hepatic failure. She had been in good health until seven months before admission when she developed heat intolerance, tremor, weight loss, and palpitations. A clinical diagnosis of hyperthyroidism was confirmed by the findings of a free thyroxine (FT_4) level higher than 7 (normal range 0.9–2.1 ng/dL) and a thyroid-stimulating hormone (TSH) level lower than 0.1 (normal range 0.8–5 mU/L). Total bilirubin was normal at baseline, whereas aspartate aminotransferase (AST) and ALP levels were slightly elevated (Table 1). A course of PTU at 300 mg per day together with propranolol was initiated, after which the patient improved clinically while her FT_4 level decreased. Four and one-half months later, however, she presented with jaundice, abdominal pain, and signs of acute hepatitis (Table 1). Serology testing for hepatitis A and B viruses was negative. PTU and oral contraceptives were discontinued, and the patient's hyperthyroidism subsequently worsened. A radioactive iodine (RAI) uptake examination of the patient's thyroid gland revealed 75% uptake at 5 hours and 68% at 24 hours, and she was treated with RAI (28.3 mCi of ^{131}I) for thyroid ablation.

Three weeks after RAI treatment, the patient was readmitted to the hospital with fever and tachycardia. Her FT_4 level was higher than 7.5 ng/dl and her liver function had deteriorated. A workup for infection yielded negative results, and propranolol was replaced with atenolol. She was transferred to UCSF for further treatment.

The patient had no significant past medical illnesses except for a cholecystectomy performed two years previously. She had no history of liver disease, alcohol use, transfusion, drug abuse, or exposure to hepatitis, and no family history of liver disease. Her medications at the time of transfer included atenolol and cefotaxime. On physical examination, the patient was thin and markedly icteric but awake and oriented. Her blood pressure was 136/70 mm of mercury and her pulse rate was regular at 110 beats per minute. She was afebrile. Eye examination revealed slight proptosis with no lid lag or stare. The patient's thyroid gland was diffusely enlarged (approximate weight 50 g), mildly firm, and tender. A thyroid bruit was present and breath sounds were decreased at both lung bases. Cardiac examination showed a hyperdynamic precordium with tachycardia. Her liver and spleen were not palpable. Her liver span was 9 cm, and mild right upper quadrant tenderness and ascites were present. Pitting edema of both legs was noted. There was no asterixis.

Laboratory investigations showed a hemoglobin count of 8.8 mg%, a leukocyte count of 5,200 per mm^3,

Table 1.—*Results of Thyroid and Liver Function Tests*

Time	FT_4 (0.9–2.1) ng/dl	FTI (6.5–12.5)	T_4 (5–11) µg/dL	T_3 (95–190) ng/dL	TSH (0.4–4.8) µIU/ml	TB (0.1–1.2) mg/dl	ALP (41–133) U/L	ALT (2–54) U/L	AST (2–39) U/L	PT/INR (10.7–14.0) sec
Before admission										
7 mo	>7.0				<0.1	1.1	216		50	
	PTU was started									
6 mo	3.7				<0.1					
5 mo	2.0				<0.1					
4 mo	0.5				<0.1					
2.5 mo	1.7				<0.1	15.0	205	942	715	14.5/1.5
	PTU was discontinued									
2 mo	>7.4				<0.1	12.8	148	588	540	14.3/1.4
1.5 mo	28.3 mCi of ^{131}I was given									
2 wk	>7.5				<0.1	22.0	212	158	238	15.5/1.7
Admission		29.3	12.6	444	<0.05	24.1	107	102	197	14.7/1.5
1st wk	Dexamethasone and SSKI were started					23.4	141	245	217	16.8/2.0
2nd wk		15.8	9.5	273	0.09	21.9	186	210	119	18.4/2.4
3rd wk		7.4	4.5	109	<0.05	19.9	242		155	14.5/1.5
4th wk		6.9	4.6	138	<0.05	10.7	227		95	14.3/1.4
5th wk		7.7	4.3	168	<0.05	4.5	173		81	14.8/1.5
	SSKI was discontinued									
6th wk		6.5	4.2		<0.05	2.6	149	20	40	13.3/1.2
6th mo		7.9	8.3		<0.05	1.0	184	25	29	12.2/1.0
9th mo		4.2	6.5		34.1	0.5	119	29	31	
24th mo		8.7	14.0	128	4.0	0.5	77	30	26	

FT_4 = free thyroxine; FTI = free thyroxine index; T_4 = thyroxine; T_3 = triiodothyronine; TSH = thyroid stimulating hormone; TB = total bilirubin; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST: aspartate aminotransferase; PT = prothrombin time; INR = international normalized ratio; PTU = propylthiouracil; SSKI = saturated solution of potassium iodide.

and a platelet count of 30,000 per mm^3. Electrolytes, renal function, glucose, calcium, and phosphorus were all normal except for hypokalemia. The results of liver and thyroid function tests are shown in Table 1. Hepatitis serology testing for hepatitis A, B, Epstein-Barr virus, and cytomegalovirus was negative. Hepatitis C virus serology was not available at the time of the patient's illness. Ultrasonography examination of the abdomen revealed normal liver and spleen size with ascites, bilateral pleural effusions, and no evidence of biliary obstruction.

The clinical impression was thyrotoxicosis and severe hepatic failure caused by PTU. The patient's thyrotoxicosis was thought to result from Graves' disease, with a possible contribution from RAI-induced thyroiditis. She was started on a course of dexamethasone (4 mg twice a day). A thyroid uptake/scan was attempted, but significant background interference from prior therapeutic ablation made the results difficult to interpret. The patient's 3.5-hour uptake was 43% and her 24-hour uptake 36.7%. To treat her thyrotoxicosis, a course of saturated solution of potassium iodide (SSKI) (5 drops administered orally twice a day) was initiated. Supportive therapy and atenolol administration were continued. Her liver function continued to worsen, however, and coagulopathy developed. Subsequently the liver transplant service was consulted. A liver biopsy specimen, obtained three months after PTU was discontinued, showed bridging fibrosis, bile duct proliferation, and ongoing hepatocyte necrosis consistent with recent injury that had progressed to cirrhosis. There was no histologic evidence of viral or autoimmune hepatitis or α-1 antitrypsin deficiency. Because of her grim prognosis, the patient was placed on a waiting list for liver transplantation.

After one week of dexamethasone and SSKI therapy, however, T4 and T3 levels started to decrease, and a week later her liver function began to improve steadily (Table 1). Dexamethasone therapy was tapered and stopped. Supportive care continued, and a liver biopsy revealed changes consistent with regeneration. The SSKI regimen was discontinued after four weeks of treatment. The patient's condition improved and she was discharged from the hospital six weeks after admission. Two weeks later, recurrent hyperthyroidism was noted and she received RAI therapy (19.6 mCi) on an outpatient basis. Results of physical examinations of the liver and spleen were unchanged. She subsequently developed hypothyroidism, and thyroxine replacement therapy was started. Her liver function has remained normal (Table 1).

Discussion

It has long been known that the physiological functions of the thyroid gland and the liver are interrelated. Thyroid hormones regulate many cellular activities,

including growth and development, metabolism of nutrients, temperature regulation, and oxygen consumption, most of which occur in the liver. Thyroid hormones are also necessary for some liver functions, such as bile acid metabolism and bilirubin transport and excretion.[14,15] Because it is a primary site of thyroid hormone activity, storage, and metabolism, the liver plays an important role in the physiology of thyroid hormones.[16] In addition, the three major thyroid hormone transport proteins—thyroxine-binding globulin, prealbumin, and albumin—are all synthesized by the liver.

Before an effective treatment for hyperthyroidism was developed, severe hepatic dysfunction and jaundice were common in patients with long-standing cases of this disease. Several pathological findings of the liver have been described in cases of long-standing thyrotoxicosis.[17,18] With the advent of antithyroid drugs and RAI therapy, severe hepatic dysfunction has become a rare complication of thyrotoxicosis, although subtle biochemical changes are still commonly observed.[19] Transaminase enzymes are elevated in 23 to 67% of uncomplicated hyperthyroid cases,[2,3,19,20] whereas serum total bilirubin levels are elevated in 5 to 50% of patients with thyrotoxosis.[3,19] The finding of increased ALP levels reported in association with thyrotoxosis has been attributed to increased osteoblastic activity, since the bone ALP isoenzyme predominates and 5'–nucleotidase levels are normal.[19,21] In our patient, the slightly elevated ALP and alanine aminotransferase levels found at initial diagnosis were consistent with changes resulting from hyperthyroidism.

The mechanism by which thyroid hormones cause hepatic dysfunction has not been established. In cases in which hepatic dysfunction occurs in the absence of heart failure, malnutrition, or sepsis, other mechanisms have been proposed. First, thyrotoxicosis may result in focal hepatic hypoxia, because thyroid hormones induce a hypermetabolic state by increasing tissue oxygen demand. In hyperthyroidism, hepatic oxygen consumption increases, whereas hepatic blood flow remains constant.[22] This could result in relative hypoxia in centrilobular zones of the liver, resulting in liver injury. Second, the hyperthyroid state may unmask underlying liver disease. For example, hyperthyroidism has been reported to aggravate Gilbert's disease,[4] possibly by competition between thyroxine and bilirubin for glucuronide conjugation and biliary excretion.

In the present case, hepatic failure occurred during PTU therapy. Hepatotoxicity is a well-described but rare complication of antithyroid drugs. Treatment with PTU can cause acute hepatocellular necrosis, whereas methimazole and carbimazole are potential causes of cholestatic jaundice.[9] Approximately 30 cases of PTU-induced hepatitis have been documented in the English language literature.[9,23–28] The mechanism of PTU-induced hepatic injury is not fully understood, although it may result from a hypersensitivity reaction. In one series, duration of PTU therapy before the onset of overt hepatitis varied from one day to five months, and the clinical course also varied widely.[9] Most of the patients improved after discontinuation of PTU, although fatal cases of PTU-induced hepatic failure have been reported.[10–13] Subclinical hepatic injury from PTU without signs and symptoms of hepatitis or hyperbilirubinemia is much more common.[29] The histologic findings in liver biopsy specimens obtained in these patients differ from those in patients with overt hepatitis, which suggests a different underlying mechanism.

The present case is notable for the resolution of severe PTU-induced hepatic dysfunction after resolution of thyrotoxicosis. The patient's hepatic dysfunction persisted for three months without signs of recovery after discontinuation of PTU therapy, but resolved after her thyrotoxicosis abated. In animal models, treatment of hyperthyroidism improves hepatic function. In rats, control of hyperthyroidism by thyroidectomy or thiouracil therapy prevents hepatic necrosis associated with dietary deficiencies[30] as well as liver toxicities caused by carbon tetrachloride and acetaminophen.[31–33] Chronic alcohol consumption induces a hypermetabolic state similar to hyperthyroidism, whereas reduction of thyroid function by thyroidectomy or PTU abolishes the hypermetabolic state and reduces histologic changes in the rat liver.[34,35] In humans, however, supportive evidence for the therapeutic benefit of the aforementioned treatment options is less substantial. Several reports have documented the resolution of hepatic dysfunction after treatment of thyrotoxicosis.[4–8] Greenberger et al.[4] reported four patients with thyrotoxicosis and jaundice in the absence of heart failure whose hepatic dysfunction resolved after they became euthyroid. Yao and colleagues[7] described a patient with cholestatic jaundice who was found to have hyperthyroidism after extensive workup. Six days after RAI treatment, the patient's serum total bilirubin decreased, and jaundice gradually resolved. Two case reports have described hepatic dysfunction in patients with hyperthyroidism induced by subacute thyroiditis, which resolved after thyroid function normalized.[5,6]

In our case, it is unclear how the control of thyrotoxicosis resulted in the resolution of hepatic failure. In severe hepatic dysfunction, thyroid hormone metabolism and excretion are impaired. The hepatic uptake of T3 and T4 diminishes and production of thyroxine-binding protein is reduced, resulting in high plasma free hormone concentrations that may aggravate thyrotoxicosis. Insofar as hyperthyroidism is known to cause hepatic dysfunction, it may lead to a vicious cycle involving hyperthyroidism, hypoxia, and worsening hepatic function. Once hyperthyroidism is treated, hypoxia diminishes and hepatocytes begin to regenerate and regain their normal functions. Our case illustrating the resolution of hepatic dysfunction after treatment of thyrotoxicosis suggests that controlling hyperthyroidism may be beneficial in such patients.

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Trimethoprim-Sulfamethoxazole Associated With Hyperkalemia

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TRIMETHOPRIM-SULFAMETHOXAZOLE (TMP-SMX) is a broad-spectrum, fixed-dose combination antimicrobial medication that is commonly used to treat a variety of infections. The drug consists of one part TMP to five parts SMX and is available in oral and intravenous formulations. Trimethoprim-sulfamethoxazole prevents bacterial synthesis of tetrahydrofolic acid, thereby interfering with bacterial nucleic acid synthesis.[1] The drug is active against a broad range of gram-positive and gram-negative organisms and is inexpensive compared with other widely used antibiotic drugs. As a result, TMP-SMX is quite popular in everyday medical practice, especially for infections of the urinary and respiratory tracts. Side effects, however, are not infrequent; the most common are rash and gastrointestinal distress.[1] Recently there have been reports of hyperkalemia as a complication of TMP-SMX therapy in patients without acquired immunodeficiency syndrome in whom TMP-SMX–induced hyperkalemia is quite common.[2–4] Dangerous hyperkalemia has been reported in patients treated with standard oral doses of TMP-SMX alone,[3,5–7] or in combination with spironolactone[8] or enalapril.[4] The mechanism of TMP-SMX induced hyperkalemia is the similarity of TMP to the potassium-sparing diuretic, amiloride.[9,10] We report the case of an elderly man who developed hyperkalemia soon after initiation of TMP-SMX therapy for a urinary tract infection. The hyperkalemia promptly resolved after discontinuing the drug.

Report of a Case

This 81-year-old man with a history of noninsulin-dependent diabetes mellitus, hypertension, and coronary artery disease was admitted to an inpatient physical medicine and rehabilitation unit after sustaining an arch fracture of the first cervical vertebra. The patient had been doing well until he fell in his home, causing a fracture involving the arch of C-1 and the facet between C-1 and C-2. After placement of a temporary cervical halo, he did well postoperatively and was eventually transferred to the rehabilitation unit, where he was able to

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walk with assistance and received daily physical therapy. After approximately 1 week on the unit, he complained of dysuria. He was placed empirically on oral TMP-SMX (80 mg TMP and 400 mg SMX) administered orally twice per day while awaiting urine culture results. He had no fevers, chills, hematuria, flank pain, or other complaints. He had no history of renal failure or adrenal disease. His medications included glyburide 5 mg twice per day, digoxin 0.125 mg daily, benzapril 10 mg daily, and metoprolol 25 mg twice per day.

The patient's vital signs were normal and he was afebrile. General physical examination was unremarkable. Urinalysis revealed pyuria and bacteruria but no proteinuria or ketonuria. His complete blood cell count was normal, as was the differential. Two days before commencing TMP-SMX therapy, his routine laboratory values were as follows: sodium 133 mEq/L, potassium 4.7 mEq/L, chloride 101 mEq/L, bicarbonate 21 mEq/L, blood urea nitrogen 30 mg/dl, creatinine 1.1 mg/dl, anion gap 11, and glucose 178 mg/dl. Calcium, phosphorus, and liver function tests were normal. The next day, urine culture revealed more than 100,000 colonies of *Eschericha coli*, which was susceptible to TMP-SMX. Two days after commencing treatment with TMP-SMX, however, a routine electrolyte panel revealed a serum potassium level of 5.3 mEq/L. The patient continued to receive TMP-SMX while his serum potassium level increased to 5.4 mEq/L and 6.3 mEq/L, respectively, during the next 2 days. His serum creatinine levels remained normal with normal urine output, and there was no evidence of hyperchloremia, making urinary obstruction unlikely. His urine pH was 5 and the digoxin level within therapeutic parameters. There was no evidence of leukocytosis, thrombocytosis, or erythrocytosis, which may have accounted for pseudohyperkalemia; furthermore, there was no evidence of hemolysis in his blood specimen. Although an electrocardiogram revealed no peaked T waves, 30 g of sodium-polystyrene sulfonate was administered and the TMP-SMX was discontinued. During the ensuing 2 days the patient's serum potassium level decreased to 4.3 mEq/L and remained normal thereafter.

Discussion

Hyperkalemia is a potentially life-threatening condition that may cause ventricular irritability leading to cardiac arrest and death. Many commonly used drugs have been implicated in causing hyperkalemia, including potassium supplements, heparin, nonsteroidal anti-inflammatory agents, angiotensin-converting enzyme inhibitors, potassium-sparing diuretics, beta-adrenergic antagonists, and penicillins.[11,12] Recently, there have been a growing number of case reports[2–4,8] and letters to the editor[5–7] linking hyperkalemia with TMP-SMX. Perlmutter et al.[3] reported a case of TMP-SMX induced hyperkalemia in an elderly woman whose serum potassium level reached 9.3 mEq/L; this patient was not on any other drug regimens. A case was also described in which a patient who was being treated concurrently with TMP-SMX and the potassium-sparing diuretic, spironolactone, developed severe hyperkalemia with bradycardia and QRS complex widening.[8] Another report described a patient who received TMP-SMX in addition to enalapril and developed hyperkalemia (serum potassium level 6.8 mEq/L).[4] Because hyperkalemia is a well-known adverse effect associated with ACE inhibitors and spironolactone, it is not surprising that dangerous hyperkalemia sometimes results when drugs from these classes are administered in conjunction with TMP-SMX. The patient presented in this report showed no evidence of other causes of hyperkalemia, such as acute renal failure, pseudohyperkalemia, digoxin toxicity, type IV renal tubular acidosis, or excess potassium administration. Urinary tract obstruction may result in hyperkalemia; however, the creatinine level in our patient remained normal as did the urine output. However, he was given benzapril, which may have predisposed him to hyperkalemia.

The mechanism of TMP-induced hyperkalemia is the similarity of TMP to the potassium-sparing diuretic, amiloride.[9–11,13] Trimethoprim is structurally similar to amiloride, and both are organic cations. Amiloride's principal site of action in the kidney is the distal tubule, where it inhibits potassium secretion by blocking sodium channels on the luminal side of the cell.[10,13] The action of TMP is similar to that of amiloride; like amiloride, it blocks apical sodium channels on the distal renal tubular cell, which reduces transepithelial voltage and leads to inhibition of potassium secretion. Velazquez et al.[9] performed renal microperfusion studies in rat distal kidney tubules and showed that TMP inhibited potassium secretion by 59%.

Clinical studies have also shown that TMP-SMX causes hyperkalemia in patients treated with standard doses. Alappan et al.[14] recently studied the effects of TMP-SMX on potassium homeostasis in 80 hospitalized, immunocompetent patients with various infections. They found that the standard dose of TMP-SMX (TMP <320 mg/day; SMX <1600 mg/day) increased serum potassium level in their patients by 1.21 mEq/L an average of 4.6 days after initiation of therapy compared with controls treated with other antibiotic medications. Peak serum potassium levels higher than 5 mEq/L occurred in 63% of the patients in their study and levels above 5.5 mEq/L occurred in 21%.[14] Elderly patients may be at increased risk of TMP-SMX–induced hyperkalemia becasue of polypharmacy and an age-related decline in glomerular filtration rate.[11,15]

Despite the fact that its use is commonly associated with hyperkalemia, TMP-SMX remains an underappreciated cause of this side effect in bedridden as well as ambulatory patients, especially among the elderly.[2,3,11,14] Because hyperkalemia is potentially life threatening, clinicians who use this drug should be aware of this important side effect, and should administer it with caution in the elderly and in patients concurrently receiving other drugs known to affect potassium balance.

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Editorial

Treatment of Chronic Severe Asthma

In this issue, Mancinelli, Navarro, and Sharma report the efficacy of a treatment for a group of patients for whom an effective treatment is clearly needed. The group was of patients with frequent emergency department visits and hospitalizations for asthma despite regular treatment with prednisone. Patients with such severe disease make up a small proportion of the asthmatic population but account for a disproportionate share of asthma's economic costs[1] and mortality.[2] These patients are caught between the certainty of morbidity from asthma on the one hand and the likelihood of severe toxicities from the customary therapy of systemic corticosteroids on the other. Many alternative therapies have been proposed, including not only the treatment that Mancinelli et al found effective—intramuscular injection of triamcinolone[3–5]—but also other "anti-inflammatory" agents such as methotrexate,[6] gold,[7] cyclosporine,[8] and troleandomycin.[9]

See Article, pages 322–329

Publication of studies of each of these agents for severe, steroid-dependent asthma provoked skepticism on two points: first, that the usual causes of poor asthma control had not been searched for and treated; and second, that it was the greater attention to the details of care by both patient and physician, rather than the additional therapy, that accounted for the improvement. Mancinelli et al's paper will evoke the same response.

Before a patient's asthma can be considered unresponsive, or even poorly responsive, to standard therapy, several conditions must be fulfilled. The first and most important condition is that the patient understand and adhere to the treatment regimen. Disease-management programs that emphasize education and compliance have had effects on hospitalization rates as dramatic as those reported by Mancinelli et al.[10] If asthma is inadequately controlled even after careful attention has been paid to education and compliance, special studies should be done to exclude the co-existence of conditions that mimic (principally vocal cord dysfunction[11]) or worsen (principally sinusitis or gastroesophageal reflux[12,13]) asthma. Mancinelli et al emphasize that the patients in their study had been under their own care for many months or years before they were enrolled in their study, so the necessary diagnostic studies had presumably been done. One cannot presume, however, that the patients were receiving maximal therapy: their doses of inhaled corticosteroids were low,[14] and none had been prescribed the high-dose formulation of fluticasone that has been reported to be remarkably effective in weaning patients from prednisone.[15] Additionally, none appears to have been prescribed salmeterol, the long-acting agonist now shown in several studies to confer a greater additional benefit to regular use of an inhaled corticosteroid than does doubling the dose of the inhaled corticosteroid.[16,17]

Mancinelli et al acknowledge the possibility that it was the greater attention to the details of care that accounted for the improvement brought about by intramuscular injection of triamcinolone, but their dismissal of the "Hawthorne effect" as contributing to their findings is unpersuasive. One clue that their patients may not have been taking their medications regularly is that only 5 were reported to have had abnormally low serum cortisol levels despite a reported average prescribed dose of prednisone of 14.4 mg/day for a mean period of 9 years, with 10 patients prescribed 20 mg/day for at least one year before entry into the study. The improvement after intramuscular injection of triamcinolone may thus reflect nothing more than an assured systemic delivery of exogenous corticosteroid coupled with improved adherence to the regular use of inhaled corticosteroid therapy. Patients with asthma comply poorly with inhaled corticosteroid therapy,[18] and Mancinelli et al's patients may have been stimulated to improve their compliance by the formal ritual of entry into a research study. The power of enrollment into a research study in improving asthma has been recognized long enough to provoke the aphorism that "the best therapy for patients with severe asthma is enrollment in a research study." An example is Lacronique et al's study of the effectiveness of a high-dose corticosteroid inhaler in patients who had required daily prednisone for two or more years: 76% of those assigned the high dose inhaler were weaned from prednisone, but this was also true of 34% of the subjects assigned placebo inhalers.[19] Studies of new therapies for asthma simply must be done prospectively and with concurrent controls.

As for the therapy itself (as the authors again acknowledge), the use of intramuscular injection of triamcinolone has been reported in previous studies of severe asthma.[3,5,20] The initial enthusiasm for this approach was tempered by follow-up of the patients, revealing a high rate of corticosteroid-related toxicities, particularly steroid myopathy,[21] that became apparent only after several months of therapy. The IM injection may thus do no more than guarantee systemic delivery of a potent corticosteroid, for good and ill. Its use should not replace the careful search for complicating conditions and detailed attention to the measures that improve compliance with therapies of proven efficacy and minimal toxicity.[22]

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Special Series—Introduction

A Few Words About *The Quest for Mercy*

Roger Bulger, MD, FACP, is a man with a good memory and a great heart. Last year, we wrote several colleagues to announce that The Western Journal of Medicine had weathered its time of troubles and to request that they keep the journal in mind when they wrote papers of exceptional merit. Dr. Bulger remembered that letter as he prepared the manuscript of a book on mercy and managed care. Reviewers urged him to seek wide distribution of the finished piece, perhaps via the lay press. He thought the journal would be a better venue since his work is aimed at physicians and other clinicians, including young physicians and medical students. His goal is to engage more than those in medicine, however. He also hopes to touch patients, families, policymakers, and indeed the public as a whole.

Dr. Bulger's book addresses managed care and managed cost, of course. It also addresses sickness and healing, hope and despair, relationships, oaths, populations, prevention, and patients. In an afterward, Dr. Bulger discusses the tensions between idealism and reality, between our profession and our lives.

Dr. Bulger writes with authority and passion. He trained in medicine at the University of Washington and Harvard, was medical director of the University of Washington Hospital, and then served on the faculty at Duke University Medical Center before he became Executive Officer of the Institute of Medicine of the National Academy of Sciences, Chancellor and Dean of the Medical School at the University of Massachusetts at Worcester, President of the University of Texas Health Sciences Center at Houston, and now, President of the Association of Academic Health Centers in Washington, D.C. He has published scores of papers and chapters, as well as three books on subjects ranging from infectious diseases to medical education, humanities, Hippocrates, and, not surprisingly, academic health centers. He is invited to speak throughout the world. His authority and passion come not only from his life in academia and practice. He is also a patient who has dodged a fatal bullet not only once, but, we hope, twice.

This is part one of three that will be published in The Western Journal of Medicine in November and December 1997 and January 1998. What a splendid way to give thanks, to celebrate the holidays, and to start a new year. The entire book will be published by Carden Jennings Publishing Company, Inc., (1224 West Main St., Suite 200, Charlottesville, VA 22903-2858; (804) 979-8034; fax (804) 979-4025; e-mail wjm@cjp.com) and available for $10.00. Its price is low because it is partly subsidized by support from the John P. McGovern Foundation.

This book will become a classic. Eric Cassell recently listed some of his favorite medical books as he exhorted physicians to read them.[1] He noted that physicians of course need to know about the march of molecular medicine, pathophysiology, and modern diagnosis and treatment. He said that physicians also need to put patients, not just diseases or organ systems, at center stage. They need to understand health as well as sickness, souls as well as bodies, meaning as well as behavior. I would add that physicians need to know themselves, to review their values, and to refresh their energy, especially now. I would therefore endorse the following books to accompany Dr. Bulger's as we join together in the noble quest for mercy:

- *The Plague* by Albert Camus (Random House)
- *Man's Search for Meaning* by Viktor Frankl (Simon and Schuster)
- *Self Renewal: The Individual and the Innovative Society* by John W. Gardner (WW Norton and Co., revised)
- *The Way of Life. An American Version* by Lao Tzu (Putnam Publishing Group)
- *On Doctoring: Stories, Poems, Essays* edited by Richard Reynolds and John Stone (Simon and Schuster)

I hope this series will lift you as you read, reflect, recall, renew.

Linda Hawes Clever, MD

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SPECIAL SERIES—PART I

The Quest for Mercy
The Forgotten Ingredient in Health Care Reform

ROGER J. BULGER, MD, *Washington, DC*

Preface

This book is about medicine and the caregiver in today's society. I have written it from the perspective of an educator deeply involved in practicing and teaching medicine for almost thirty-five years. At first, I had only younger and future colleagues in mind. As the book progressed, however, I also attempted to make it a work of interest to anyone concerned with his or her own health in particular and with health care reform in general.

Health care is a wonderful calling because it involves the professional in all aspects at both extremes and along the full continuum of life's experiences. But on occasion over the years, I have found myself in circumstances demanding actions that have challenged the boundaries between my various life roles (physician, husband, father, son, brother, citizen, friend). The appropriate responses, however, were not articulated in medical textbooks. I wish that, as a medical student and young physician, I had been provoked to ponder some of the less concrete and less technical aspects of physicianhood—for example, dealing with the joy, birth, healing, growth, suffering, pain, separation, and death that I discuss in the following pages. They are compelling but often overlooked aspects of clinical practice that arise in one form or another every day.

During the course of writing this book, I suddenly found myself cast in yet another role. This time I was a patient. Furthermore, I was a patient with a complex, serious disease. My perspective on our health care system changed dramatically.

Health care reform is bringing about a complete turnaround in the financial incentives available to providers: previously paid for each intervention they performed, many are now paid to minimize their interventions, and sometimes not to intervene at all. As a result, the primary objective for many providers today may be cost containment. Does this mean that the growing prospective payment, capitated care system will so alter provider payment mechanisms that the core financial incentives for caregiving will become completely reversed?

Furthermore, since recent health care reform is also largely changing the method of rationing professional time, those caregivers whose time is excessively restricted may well lose altogether the time it takes to develop the trust that, in turn, empowers patients to enter into their own healing.

I believe my own recent experience was highly positive, in part, because I never questioned the motivations of my caregivers, never worried that they had incentives to keep valuable treatments from me even when the prospects of full recovery were unclear. Thus I believe we must find a way to restrain clinical costs without twisting the caregiver's motivation to help the patient and without driving a wedge between the sufferer and the healer.

There is an order to the sequencing of the subjects I discuss in the following pages. The left side of my brain can argue that this ordering is rational, with each chapter flowing from the preceding chapter until the story emerges of what it takes to make a full-blown healer. In all honesty, however, I can only say that the chapters represent pieces to a puzzle that, if put together in any order through an individual's educational life experiences, represent the essentials of the mature, twenty-first century scientific healer, no matter how or when the essentials are acquired.

I use the term "scientific healer" to recognize that there are other "healers" out there who seem capable of eliciting a suffering person's own healing powers. Modern medicine, however, empowers its practitioners with many enormously effective scientific interventions that, if grafted onto the elements of being a healing person, open up extraordinary capacities to benefit people.

I start with the difference between illness, disease, and suffering; the peculiarly American slant that we bring to the condition of suffering; and some first-hand experiences of physicians as patients (including myself) in section I.

Because understanding and easing the suffering of a patient can eventually be only as effective as the care-

(Bulger RJ. The quest for mercy: the forgotten ingredient in health care reform. West J Med 1997; 167:362–373)

From the Association of Academic Health Centers, Washington, DC.
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giver's communication skills, section II (coming in the December issue) discusses these skills; they form the basis of a trusting relationship with the patient, and also facilitate the patient's self-healing capacities. The second section also examines the essentials of the Hippocratic oath, the placebo effect, and some literature relating to self-healing. Seldom are therapeutic victories complete, however, and the true healer understands this fact of life almost instinctively. Thus, I also point out that whereas a return to full health can happen in one patient, perhaps the best outcome in the next patient leaves chronic debility or permanent loss. Just as this patient now needs to cope with a new reality, the caregiver must be certain the patient is not abandoned.

Section III (coming in the January issue) deals with the tensions among the new, growing population-based emphasis on health status, health promotion, and disease prevention; the reductionist, biomolecular, disease-oriented paradigm that rules among most medical school faculty today; and the biopsychosocial paradigm, which takes the patient's feelings into account and seeks to bring the behavioral sciences to the relationship between patient and clinician.

In section IV (coming in the January issue), I explore the traditional relationship between patient and healer, and the new conflicts of interest and ethics that caregiving health professionals are beginning to face in these rapidly changing times. A revision of the Hippocratic oath is suggested that better mirrors the world in which tomorrow's caregivers will be rendering care. Thus, by analogy and extension, we come to the concept and characteristics of a therapeutic team of health professionals. (Today, of course, this health care team includes the patient.)

Note that almost all of my generalizations about the individual clinician refer to whatever collection of people and entities become part of what I call an "organized healing delivery system." But however we conceive of or refer to the way we provide health care in America, the next century must see us, the caregivers, improve both our individual and our collective performances as therapeutic agents. Only in this way can we bring humanity into our ever-increasingly technology-dominated enterprise.

I believe that health care is a career that can marry marvelously the worlds of action, emotion, and mind. It remains one of the most rewarding careers available. Little more can be asked of a professional life. I hope this book makes the reader aware of the extraordinary breadth of interest and scholarship open to thinking caregivers who keep learning from a wide array of disciplines. I also trust that caregivers, policymakers, and the general public—potential patients all—will find food for thought in the following pages as America reflects on a health care system in flux.

Section I—Why Patients Need Healers

Chapter 1

Understanding Illness, Disease, and Suffering

We spend much of our lives trying to avoid, ignore, or minimize suffering—but sooner or later it finds all of us. Suffering is part of the human condition. Caregivers, especially doctors and nurses, have a dramatically larger experience with suffering than others because they minister to those suffering people we call patients, a word that connotes suffering or endurance. In fact, I believe that you are not a patient if you are not suffering, and you cannot be an effective caregiver if you do not know a great deal about suffering and its alleviation.

The Connection and the Distinction

How do disease and illness connect to the concept of suffering? Simply put, disease plus suffering equals illness! There is a rich distinction between the two terms, disease and illness. A disease can be labeled (for example, diabetes, multiple sclerosis, tuberculosis, or breast cancer). The label typically refers to an identifiable pathologic state with a known or unknown cause, a pattern of symptomatic involvement and diagnostic laboratory tests, a describable clinical course, and a range of known courses that has been established by following the lives of previous patients. In each case, the hope is that a physiologically or molecularly precise, effective, and safe treatment will be discovered and made widely available.

Beyond Physical Pain

Illness, on the other hand, describes how that disease affects a particular patient because of that patient's life experiences, including the patient's ethnicity, age, sex, family, and sociocultural situation. The person's underlying emotional state and emotional response to the disease have a great influence on the illness. Understanding an individual's illness is essential to estimating the degree of suffering the patient is experiencing and, in turn, to establishing a method for helping the sufferer deal with the illness.

Fear of Death

Let me provide a simple example. From my own experience as an intern and resident, I concluded early on that virtually every patient who entered the hospital must be worrying about the increased possibility of

dying, either from the disease, or the treatment, or the errors inherent in the health care system. Thus, while focusing on a particular disease, I found it extremely useful to anticipate these broader fears, recognizing and discussing them with the patient. The patients, I believe, were much happier and more confident in me because I foresaw and empathized with their concerns; they experienced less fear and anxiety from the hospitalization than otherwise would have been the case.

Because the disease/treatment environment can add to either the patient's illness burden or relief, caregivers need to anticipate all the forces affecting the patient's life and try to alleviate as many negative ones as possible. The most effective physicians are those who can combine their science-based competencies at diagnosing and treating disease with the capacity to join with the patient in combating the broader issues of illness and suffering.

Loss of Control

Although there are many different notions of suffering, there is an unusually strong convergence about the ultimate meaning of suffering. Eric Cassell, a physician, articulates this generally held meaning best when he describes suffering as a state of distress induced by the loss, or threatened loss, of control or meaning in one's life, or by the perceived disintegration of one's persona. Suffering, he asserts, is a feeling that goes beyond and is distinct from pain. Two persons may be exposed to the same pain, but suffer to different degrees. Suffering may also occur in the absence of pain, as in the anticipation of future pain. Cassell emphasizes the social and psychological foundations of suffering: "Suffering is a consequence of personhood—bodies do not suffer, persons do."

Dread of Abandonment

John Fortunato, in his recent discussion of the spiritual dilemma that the AIDS epidemic has forced upon society, underscores the idea of the sufferer being excluded, or feeling isolated, from society. He describes how an individual's suffering heightens when societal support systems seem to wither away as death becomes inevitable. Pediatrician R. Vieth also deals with these ideas in terms of their theological implications; I include such theological considerations in this discussion because many people in our society are influenced by them.

My own experience with a severely psychotic patient, whom I met when I was a fourth-year medical student, showed me how isolation itself can cause suffering. The patient rambled unintelligibly and people thought that she was hallucinating, a situation that hindered human interaction and increased this woman's isolation. As I came to know her, and explain more fully in chapter 4, I came to understand her vision of herself as an abandoned princess; my understanding helped to end her isolation and begin the long journey toward improving her health.

Anthropologist Margaret Mead has also equated suffering with exclusion from society, concluding that to reduce suffering as well as to increase the strength of society, all suffering citizens must be included in the fabric of society. Implicit in this argument is the assumption that a strong society takes care of its weakest members. As the poet William Blake wrote, "The dog starv'd at his master's gate/Predicts the ruin of the state."

Loss of Esteem

Suffering seems infinite when self-respect is destroyed, suggests physician Howard Brody in *Stories of Sickness*. Conversely, suffering can be minimized if self-respect is maintained. In the context of these interweaving ideas, it is perhaps easier to understand how suffering accompanies grief, anxiety, depression, and other situations in which patients feel a high degree of personal inadequacy. This is why suffering strikes us all and is a universal characteristic of human life.

The suffering of Donald "Dax" Cowart, a young man recently out of the military, presents a compelling story, replete with lessons for future health professionals. As discussed by William May, an ethicist and physician, in *A Patient's Ordeal*, this young man, severely burned in a propane gas explosion, asked the first passerby to get him a gun so that he could end his own life. He asked the rescue squad not to take him to the hospital, and subsequently asked the emergency room staff not to treat him. He pleaded with anyone who would listen, "Please let me die."

Dedication

This book is dedicated to the memory of Matthew Warpick, MD, and other caregivers like him. Dr. Warpick was a physician in New York City who served generations of residents of a west Harlem neighborhood for sixty-seven years. He healed, counseled, and listened to his patients; in return, he accepted whatever they could pay. Dr. Warpick finally closed his office when violence engulfed his neighborhood and he feared for the safety of two employees. At ninety-three years old and determined to stick by his patients, whom he considered his friends, Dr. Warpick replaced the living room furniture in his apartment with an examining table and some other medical equipment, planning to see patients six days a week. "People are losing faith in doctors and medicine," he explained, "and something must be done." He believed that without ready access to friendly, caring, science-based physicians, more and more people turn to nonscience-based alternative venues in their search for caring healers. Dr. Warpick's dedication surely changed the lives of his patients. His story, as reported by Gonzales in the *New York Times*, should motivate us all, whether entering or practicing scientific medicine, to try to do the same. Dr. Warpick saw patients into his ninety-sixth year. He died in January 1997.

Acknowledgments

Because my primary concern in this book is to communicate effectively with younger people, during the writing process I enlisted the aid of three people still in their third decade of life. The first was my daughter, Grace Bulger, who is an expert on the art of communication. After reviewing my previous writings in this area and some of the relevant medical literature, she prepared an initial draft of the chapter on communication and the arts in medicine. Elizabeth Bobby spent several months working with me before beginning her education to become a nurse practitioner. She helped on the whole manuscript, but was especially involved in the evolution of the chapters in Section I. Kara Reinhardt, while an undergraduate at Princeton University, helped by giving the completed manuscript a careful reading. Her opinions and reactions led me to make a number of substantive improvements, some of them quite major.

More recently, Denise Holmes, who has become a colleague, has lent her keen intellect, insight, and editorial skills to the effort. Many thanks also go to Richard Fletcher for his design and production expertise, and to Shirley Sirota Rosenberg for her assistance in the entire editing process.

My deepest thanks also must go to my personal physicians, Bryan Arling and Bruce Kessel, who have taken care of me and helped me to do my share in addressing my illness.

My personal thanks go to the McGovern Foundation for its ongoing support of my writing efforts over the past decade. Jack McGovern has been a true friend and benefactor for over twenty years, and it is unlikely that this book would have become a reality without his interest.

Last, I must mention several colleagues who read the complete manuscript at one stage or another, and who were kind enough to offer suggestions and encouragement. I cannot blame the deficiencies on them, but readily admit that their input was vital to the shape, organization, and content of the final product.

They are Ruth Bulger, Jack Colwill, Ralph Crawshaw, Rich De Vaul, Leon Eisenberg, Elaine Larson, Sam Nixon, Marian Osterweis, Ed Pellegrino, David Rogers, John Stoeckle, and Larry Tancredi.

Dax had suffered severe burns over two-thirds of his body, including third-degree burns to his face and hands and severe damage to his eyes. Even after the initial emergency treatment, Dax's prognosis for survival remained poor. Costly, painful, extensive burn therapy continued, however, even as Dax consistently demanded that treatment be discontinued, and stated repeatedly over many months of treatment that he wanted to die.

In the story of a burn patient's painful rehabilitation, Dax's story amply illustrates profound suffering. Yet May explains how Dax's suffering was far broader than simply the physical pain of his burns:

> Short of suffering brain damage, perhaps no patient undergoes the massive alteration in self-perception and prospects that the burn victim must fear. And yet, even the burn victim and victims of other, lesser catastrophes do not suffer a total wipeout. The image of the Phoenix, risen from the ashes, partly misleads us, because the Phoenix remembers nothing of its former life. The burn victim, however, remembers his past. The persistence of memory both establishes continuity with his past but also reinforces his sense of distance from it. He remembers what he has lost and therefore grieves more deeply.

Dax's physical trauma was magnified by psychic suffering caused by the health care professionals' refusal to accede to his relentless demands. The emergency room staff assumed that he was not competent to refuse treatment and dismissed his plea as the typical reaction of a burn victim in pain. Many months later, a psychiatric evaluation found him to be competent, yet treatment continued.

May comments on how the professional's paternalistic approach clashes with the patient's autonomy:

> The provider has seen too many post-trauma depressives who have demanded that physicians stop treating them and then changed their minds later. But this suspicion of post-traumatic depressives discredits the patient's wishes and casts a long shadow into the future, particularly when the patient's opposition to a procedure seems to prove the patient's impaired capacity. The burden of proof thus effectively shifts from the physician having to justify his paternalistic intervention to the patient having to prove his competence.

Thus, the patient's physical suffering, grief, altered self-perception, depression, and anxiety about an uncertain future may be compounded by a caregiver's disregard for the patient's expressed preferences.

Parenthetically, Dax survived, pursued his education, and among other activities has remained outspoken about the conflicts inherent in his situation. As I understand it, he is happy with the life he has made since his accident, but remains adamant that he should have been allowed to die.

Chapter 2

The American Way of Suffering

A definitive analysis of our society's relationship to suffering is too complex to attempt in this short treatise. However, exploring some of the ways in which Americans may be insensitive to suffering, promote suffering, or fail to ameliorate suffering may help us reach a better understanding of American society's complex relationship with it. Because each of us is, to a significant degree, a product of our society, all aspiring health care professionals should give some thought to these matters. The study of suffering, strange as it may seem, is central to our education as caring health professionals.

Traditional Values

Life, liberty, the pursuit of happiness, individuality, and self-sufficiency: these are among the most fundamental of American values. Most people who have come to America left their own countries because they were poor, persecuted, or desperately unhappy with their governments. We are a nation with an inherent historical distrust of collectivity, especially as it is reflected in the federal government. We have had generations of success escaping initial poverty and getting out of the ghetto (although those possibilities seem to be decreasing). We have seen the progressive enhancement of our standard of living, first through westward expansion to our frontiers and then through the industrial revolution and into the postindustrial era. We believe in the benefits of individual efforts to better oneself.* We also believe that each of us should have as many years as possible to enjoy life, liberty, and the pursuit of happiness. In fact, focusing on suffering might almost be considered unpatriotic; after all, our Declaration of Independence tells us to pursue happiness. Why dwell on suffering? Better to forestall, delay, or deny it completely.

Individualism and Self-Determination

America's commitment to the individual is reflected in our health care organization and expenditure and, most clearly, in our love for the most dramatic of innovations—even if aimed at saving just one life. Our nation is capable of spending millions of dollars and riveting its collective attention for weeks on efforts to recover a child who has fallen into a well or to rescue a person lost at sea. To save a single premature infant in neonatal intensive care, we routinely spend substantial sums that could finance, if redirected, prenatal care for a large number of poor women, thereby reducing the incidences of prematurity. Psychologist Arthur Kleinman suggests that

> [P]erhaps North American culture's ideology of personal freedom and the pursuit of happiness has come to mean for many guaranteed freedom from the suffering of pain. This meaning clashes strikingly with the expectation in much of the non-industrialized world that pain is an expectable component of living and must be endured in silence.

Ben Franklin's *Poor Richard's Almanac* epitomizes Americans' reverence for individualism. "God helps those who help themselves," he wrote. Americans have taken these words to heart. In 1835, Tocqueville worried about the implications for Americans of their rampant individualism, which he saw manifested in a growing number of American frontiersmen. These men had no need for community—they believed that with their family, their gun, and their good sense and industry they could handle the world. Social scientists Robert Bellah and colleagues, in their analysis of America in the 1980s, hold that Tocqueville's concerns were prophetic. Eric Cassell agrees: "The concentration on individuality by Western culture for these last centuries . . . has obscured the more basic truth that we live in a sea of others without whom existence is literally unthinkable."

Quest for Efficiency

Organization, linear behavior, and efficiency are integral features of the American work ethic and American success in the modern era. We work hard, move from one place to another often, and sacrifice much in the name of greater efficiency, greater productivity, and greater profits. When a family member dies, we tend to limit the mourning period to one or two days and then return to work to minimize the inconvenience to our coworkers and shelve our emotions. Grieving, after all, is not productive; moreover, it disrupts the equilibrium of a finely tuned corporate system. In this context, prolonged suffering appears to thrust an unseemly burden upon others; distancing or isolating ourselves from the normal environment may seem to be the most considerate act when we are bereaved people.

The Fighting Spirit

Americans admire fighters—John Wayne, Clint Eastwood, Michael Jordan, Scott O'Grady, Martina Navratilova, even Rambo. Many of our friends, relatives, ancestors, and heroes fought their way out of poverty, ignorance, and hardship to attain better lives. Many of us may feel that God not only helps those who help themselves, but that God loves a fighter. At some level, we may, therefore, believe that people who do not fight their diseases are losers. Even children with cancer are frequently taught that defeating the disease depends on their healthy cells getting good and mad at the cancer cells. And, because a good fighter is supposed to fear nothing, we tend to hide the difficult issues posed by suffering and the concomitant fear of personal dissolution, focusing instead on the notion of bravery. Furthermore, and perhaps most destructively, when suffering cannot be avoided and death seems inevitable, sufferers may feel a failure in their efforts to ward off the disease.

Dwindling Social Ties

Our ties to the traditional societal institutions—churches, clubs, hometowns, and families—that once provided structure and support to individuals have sustained much damage in America over the last fifty years. As the sense of community diminishes, a cultural emphasis on personal privacy, individual rights, and freedoms rises. In guarding this shared sense of individuality, we seem to pay less attention to those other, more community-oriented, beliefs and values that we share.

Our voting behavior and our approach to politics have become focused on selfish desires, small groups or subsets of society, and special interests. Unfortunately, this inwardness serves to further undermine community; the larger the number of factions, the smaller the num-

* This belief, unfortunately, can also spawn the corollary perception that people who are in the midst of unfortunate circumstances either brought their problems on themselves or are too lazy to extract themselves from their quandary.

ber of groups who can achieve their goals. A case in point is the health care reform legislative debacle of 1994, in which a wide array of special interests thwarted the will of a large majority of citizens.

If suffering is a sort of separation that may be relieved by reincorporating with the group, the disintegration of social ties that link individuals to communities can only tend to make our culture increasingly unresponsive and insensitive to suffering in general. Thus, suffering gets interpreted as an individual problem, leading to an isolation that only serves to exacerbate the suffering. This seclusion, notes Eric Cassell, can further disrupt those aspects of personhood that require social contact: "Otherness is implied by self and many by one." As recognized by proponents of Twelve-Step programs and other group-centered therapies, sharing fears, feelings, and experiences can be a powerful tool for combating suffering.

Suffering as Punishment

Many Americans believe at some level that suffering is a proper punishment for sin and that the sufferer deserves to be shunned and to lose dignity in front of the rest of society. Religious belief systems sometimes contribute to this view; issues of suffering and pain are often entwined with the concept of evil in religious explanations of God's nature and intentions. Some religions teach that we deserve our suffering—that we suffer for Original Sin as well as for individual transgressions. Many religions also suggest that the evil or sin that precipitated the suffering is contagious.

Such beliefs have important implications for the sufferer. Elizabeth Heitman, who teaches in a program on humanities and technology in health care, notes that when suffering is interpreted as divine punishment, its association with evil may prompt others to reject the sufferer as contaminated. She writes, "Where suffering is interpreted as punishment, a necessary lesson, or an inevitable consequence of nature, the intervention of outsiders may be rejected as interference with the mechanisms of cosmic justice." This action, or, rather, inaction, serves to further isolate the sufferer, who has many other reasons to feel separated.

Patients whose afflictions are the result of such socially unacceptable practices as drunk driving, drug abuse, and sexual promiscuity may be more likely than other patients to have their suffering disregarded. This tendency on the part of caregivers may be especially true in settings where there are other suffering patients needing attention. It is far easier for a caregiver to feel empathy for a patient whose illness is unavoidable than for a patient who returns time and again for relief from a behaviorally induced disease.

Mass Media and Desensitization

Movies, news, and television drama series are so full of violence and death that it is rare to turn on the television without seeing or hearing about some horribly traumatic event. Explicit movies, for example, graphically illustrate how to kill, injure, or mutilate others or oneself, and the media make major figures of many of the sorriest examples of human degradation. The media not only feature violence; they tend to focus on the mundane, the material, the quick-fix, and the one-time around, thereby leaving unaddressed the suffering lurking in the background. Moreover, when suffering is portrayed on film, it is usually short-lived and often resolved in a fortunate turn of events. This casualness toward killing and death makes it easier and easier for society to minimize respect for life and more difficult to empathize with others who are suffering. We become desensitized.

Another way in which the media affect our relationship to suffering is through their love affair with wealth, fame, youth, beauty, and perfection. In the media, suffering, pain, and adjustment to adversity often seem alien to the American recipe for the good life.*

Desensitization to suffering also can occur in the health care setting. Urban, often overloaded emergency rooms are places where suffering is so common, it is no longer as appalling to the health care professionals as to persons not regularly exposed to such situations. Caregivers in general, regardless of their work setting, may be more desensitized to suffering than the general population, simply because they work daily amidst suffering. This circumstance highlights the tension inherent in a situation in which the importance of being efficient, objective, and analytical (and, in a sense, dispassionate) vies with the importance of recognizing suffering and showing compassion to those who suffer.

Reductionist View of Medicine

The Newtonian, reductionist, biomolecular orientation of modern physicianhood emphasizes scientific intervention through emphasis on the molecular causes of, and therapies for, human disease. As a consequence, this view has little to do with such concepts as the healing relationship. According to Donald Seldin, one of the great figures in modern medicine who described this view some years ago, the needs and opportunities for molecular medicine are so great that physicians should focus their energies on the pursuit of diseases in terms of their molecular causes and therapies, leaving the psyches and personalities, wants and needs, hopes and fears, social problems, and familial relationships of patients in the domain of nurses and social workers. Kleinman perceives this orientation as somewhat built into this country's view of illness:

> Social reality is so organized that we do not routinely inquire into the meanings of illness any more than we regularly analyze the structure of our social world. Indeed, the everyday priority structure of medical training and of health care delivery, with its radically materialistic pursuit of the biological mechanism of disease, precludes such

* This is not to say that the arts do not offer psychologically constructive and socially useful depictions of the true nature of suffering. As Aristotle believed, public presentations of tragedies can serve an important therapeutic function because of the emotional catharsis they engender in the audience.

> inquiry. It turns the gaze of the clinician, along with the attention of patients and families, away from decoding the salient meanings of illness for them, which interferes with recognition of disturbing but potentially treatable problems in their life world. The biomedical system replaces this allegedly "soft," therefore devalued, psychosocial concern with meanings with the scientifically "hard," therefore overvalued, technical quest for the control of symptoms. This pernicious value transformation is a serious failing of modern medicine: it disables the healer and disempowers the chronically ill.

Kleinman thus illuminates the important distinction between a disease, which can be diagnosed and treated at the molecular level, and the associated illness, which affects the whole of the patient's life and requires a broader perspective if therapeutic support is to be forthcoming.

If suffering is, in fact, a sense of impending personal disintegration, then clearly the reductionist physician described by Seldin is not predisposed to relieving emotional suffering and is likely not to be concerned with understanding or even recognizing suffering. Kleinman's view of the "technical quest for control of symptoms" points to a similar situation. In examining the Dax case, May noted that burn patients receive acute and follow-up treatment for their physical wounds, but that our society must invest more in rehabilitative and long-term care. The bottom-line message to patients and to society is one of excluding suffering from the purview of the high priests of modern medicine, those to whom we have given the vestments associated with marrying high technology with humanity. For the most part, suffering—that is, social and psychological pain—is not part of the healing equation.

Some Things We Can Do

So far in this discussion, we have emphasized the various ways in which American society ignores, denies, misinterprets, and even promotes suffering. America, however, also spends more money than any other nation on the care of the sick. This country has done as much as, if not more than, any other nation to include people with disabilities in our public and private systems. The Americans with Disabilities Act of 1990, for example, signified our commitment to integrating those with disabilities into more facets of American life. We have also brought about some of the world's most sweeping changes in disease prevention; witness smoking bans and speed limits.

Thus, America as a whole is not completely insensitive to suffering, but it could definitely enhance its sensibilities, in both a personal and an institutional sense, to suffering as a universal fact of life. Implementing prescriptions to heighten our sensitivity would be difficult and complicated. Recognizing that the insight, analysis, dialogue, and understanding necessary to undertake such a task is far beyond the scope of this discussion, I nonetheless attempt some suggestions, with the hope that they will at least offer a starting point.

Acknowledge Suffering

First, we need more discussion about suffering and its meaning in our individual lives and in our culture. A nation of optimists, expansionists, and youth and beauty idolaters, ours is a society naturally hard-pressed to think of life as a dance with illness and death. Yet, talking and thinking about suffering are important steps toward removing the taboos and restoring suffering to the human condition, as well as to the community at large. The American myth that it takes a strong will to avoid suffering needs to be reshaped to fit reality, namely, that suffering is the inescapable stuff of life that we can work to minimize and seek to prevent wherever possible but cannot completely eliminate from anyone's life. Suffering is shared by all of us and, as such, could serve as an inclusive, uniting force rather than as a divisive, exclusive, or alienating influence. Thus, instead of increasing the suffering of friends by ignoring their plight, we need to seek out such friends and help end their isolation. Acknowledging suffering does not make it go away, but it lessens a person's painful separation from the world that suffering often imposes.

Second, this nation needs to find a way to integrate its traditional values with a less superficial understanding of individuality and the concomitant hope for a long, painless, blemish-free existence unencumbered by the responsibilities of social ties. Self-sufficiency has been overemphasized; we cannot continue to neglect our need for community, especially when dealing with illness and suffering.

Health care professionals are in a good position to apply the above approaches where they are most likely to have significant impact. Indeed, their responsibility to treat illness implies the need for their attention to suffering, or the "hidden dimension of illness." The social, psychological, and even religious spheres out of which suffering is born define what it means to be ill just as do genetic aberrations and physiological malfunctions. Caregivers who work to heal by uncovering the physical origins of disease also should discover and address the fuller panoply of concerns associated with illness.

Join Behavioral and Physical Sciences

For health care professionals, a major step in addressing suffering may be to incorporate in their ethic the side of human nature that comprises the emotional, aesthetic, and spiritual dimensions of personality. The "Seldin solution" must be replaced with a broader view of science and healing and a more flexible border between the science and art of medicine. Science seems to be moving in this direction; more and more biomedical scientists are beginning to agree that expanding the paradigm beyond the Newtonian concepts should not compromise their ability to continue to mine reductionist theory for as-yet undiscovered treasure. This new movement in biomedicine—partly because of its insistence that the scientist-observer cannot only be considered an external, objective observer, but a part of the

experiment—may help bring behavioral science into full intellectual partnership with the academic health community. Movement in this direction will also expand awareness of the importance of dealing constructively and openly with suffering within the overall health care enterprise.

Health care professionals should also endeavor to educate themselves formally about suffering. The volume of literature in this area is small but, fortunately, growing as the impact of the social context of illness is increasingly appreciated. AIDS has opened up a national discussion about suffering and has helped to demystify the subject; AIDS literature, particularly that written by people with AIDS themselves, has much to teach about suffering. Those who have studied suffering have observed common phenomena of which every health care professional should be aware, namely, that the degree of suffering a person experiences has little to do with the intensity of the physical pain, and that suffering is often masked by apathy, which can reflect hopelessness rather than a lack of motivation to get better. In this regard, the work of Eric Cassell, Arthur Kleinman, nursing dean Patricia Starck, and others who have sought to understand suffering is well worth contemplating.

Physician, Know Thyself

Caregivers should also take stock of their own biases, interests, and emotions and consider how these may color their perceptions of patients and their suffering. One might ask oneself, "What constructs comprise my beliefs about suffering? That it is divine punishment for transgression? That it signifies personal weakness?" Negative childhood experiences with an alcoholic parent, for example, may have rendered you unsympathetic to the suffering of addiction. Perhaps your upbringing has instilled in you a simplistic view of the suffering of members of other racial and ethnic groups. Maybe you have a particularly high tolerance for pain or for solitude, and, therefore, risk discounting the factors that elicit suffering in others.

I know that my own excessive and immature fear of dependency on others once interfered with my ability to care adequately for quadriplegic patients. When I worked through my feelings, I improved as a caregiver. Understanding the lenses through which we view the world can help us discern more clearly the nature of the images we see through those lenses.

Health care professionals also must monitor their own physical and emotional energy levels and consider how these levels may be affecting their interactions with patients and their capacity to recognize and respond compassionately to suffering. The chaotic urban emergency room provides a salient example of a setting in which desensitization and burnout may keep professionals from recognizing suffering. Frustration and exhaustion can easily overwhelm compassion; the importance of taking time for self-renewal cannot be overemphasized.

Humanize the Environment

Institutional environments such as emergency rooms and intensive care units can also complicate the recognition and management of suffering. The whirring and beeping machines of medicine not only focus the practitioner's attention on the physiologic processes of illness, but also can intimidate patients and their families as they try to contemplate illness, loss, and perhaps even death. Caregivers should seek to minimize the negative effects of such environments, to make time and space for the low-technology, less tangible aspects of care.

When a practitioner finds it difficult or impossible to ease a patient's emotional suffering, that practitioner should be aware of other support systems in the community—other health professionals, counselors, clergy, support groups, community activities—with which the patient may be connected. Just as the caregiver follows up on biomedical interventions, he or she should also follow up on these other interventions.

Initiate and Maintain Communication

Perhaps the most overlooked, but most powerful, tool for handling suffering is communication. It sounds so simple—asking patients, in one way or the other, if they are suffering. But many caregivers apparently fail to do so. It may be that they feel their primary responsibility is to address physical conditions, a complex and exhausting task. It is more likely, however, that they shy away from addressing this issue because it is difficult and unpleasant.

The power of communication to alleviate suffering is illustrated most clearly by the practitioner clarifying a patient's erroneous belief (for example, "I'll never be able to walk again with this artificial hip") and helping this patient to understand the exact nature of the condition, treatment, and prognosis (for example, "You will be back on your feet in a matter of weeks").

Perhaps more often, an understanding and alleviation of suffering require communication at a different level—communication about the significance or meaning of an illness in an individual's life. Is the patient who has had hip replacement an active person who gets great pleasure from physical activity and independence? Could weeks of inactivity and dependence on caregivers precipitate a clinical depression? Does it matter that the patient with a particular disorder is of one particular ethnic group or another? Does it matter to the therapist if the patient is a man or a woman?

Arthur Kleinman encourages health care professionals to act as ethnographers. Writes Kleinman:

> To the extent possible, the doctor tries to understand (and even imaginatively perceive and feel) the illness as the patient understands, perceives, and feels it.... By putting himself in the position of the family members and important people in the wider social circle, the physician can empathetically witness the illness as they do. This experiential phenomenology is the entree into the world of the sick person.... The interpretation ... deepens the clinician's understanding of the experience of suffering.

Perhaps the final note about alleviating suffering should be one raised by Howard Brody, who points out that suffering is maximized when patients feel that they are not respected by caregivers and others around them. At the very least, physicians and other caregivers must show their patients that they value and respect them as individuals.

Chapter 3

The Doctor as Patient—Why Mercy?

Marcus Borg is a modern New Testament scholar whose books attempt to explore Jesus' life and words in the context of Jesus' own times. This leading biblical scholar says that Jesus called on people to treat others with compassion. Borg asserts that the word that Jesus used for compassion—wombness, as translated from the Hebrew—refers to the love of the womb and, with it, a mother's encircling concern for and support of her child; over the centuries, the term wombness has become the word mercy.

This rich meaning for the word mercy first clicked for me when I was rereading a passage from Thomas Merton's writings, in which he crystallizes the meaning of his life's spiritual journey in the words that all novitiates say upon entering the Trappist order of monks. Merton himself had uttered these words when he began his long, complex, and now very public journey into the life of the spirit. In answer to the ritual question, "What do you ask?" Merton gave the ritual answer, "I ask for the mercy of God and of the Order."

Thanks to Borg, I understand Merton's message in a new light: Merton is seeking compassion from his brothers and from God. I also have made a new connection regarding patients and the role that the health care system plays in our society. When gravely ill, suddenly disabled, or near death, even the most autonomous, independent, and strong among us seek the mercy of our society through our individual caregivers and the organized health care delivery system. Anyone may need such compassion one day.

Yet, compassion requires time. With health care time inordinately rationed today in the interest of economy, Americans could organize themselves right out of compassion.

For thousands of years, cultures have assigned high status and special designations to their healers and usually have leaned heavily on the intervention of the healer's compassionate efforts to help their patients. It would be a tragedy, just when we have so many effective scientific therapies at hand, for scientists to negotiate away the element of compassion, leaving this crucial dimension of healing to nonscientific healers. In other words, we scientifically trained healers must develop and sustain health care delivery venues that allow us to show mercy when people most need it—and that is, when they are suffering!

Facing a Life-Threatening Illness

Two years ago, my life unexpectedly entered a totally new phase. I went for a CT scan of my mediastinum (the space behind the heart). A right middle-lobe bacterial pneumonia I had experienced some months earlier was resolving more slowly than normal. To everyone's horror, the scan revealed a large mass behind my heart that seemed to encircle the right main-stem bronchus leading to the right lung. The list of possibilities included tumors that would scare anyone, and called for prompt diagnosis, which meant a thoracotomy and biopsy. The eventual diagnosis, malignant lymphoma, required six rounds of identical therapeutic interventions with three major metabolic poisons and a short course of prednisone. Five months of treatment was followed by diagnostic tests to ascertain whether I would fall among the three-quarters of patients who have a good outcome or among the significant minority who face a more difficult future.

Thus, at age sixty-one, and for the first time since age seven, I was confronting a serious illness that brought me into heavy contact with the hospital and health care system as a patient rather than as a caregiver or administrator. This time I faced a more-than-abstract possibility of fatal disease and certain involvement with a systematic biologic poisoning that would, even if all worked well and without complications, cause chronic illness for the duration of therapy and the ensuing recovery period.

Today, as I write these words some two years after diagnosis, it appears that I have fallen into the group of patients who have experienced a remission and possibly a cure (the latter, of course, to be determined by time).

A Child's View of His Illness

My only prior experience with life-threatening illness had been when I was seven and stricken with an acute streptococcal epiglottitis that required an emergency tracheostomy. It was followed by an almost fatal double pneumonia. It is said that I was saved only because of the availability of sulfanilamide (one of the first wonder drugs and the chemotherapeutic agent that preceded penicillin in the late 1930s). Meanwhile, I truly believed that I would die, because I had heard many people say so for several days, and I had had the last rites of the Catholic Church, a sacrament I well understood, having just experienced my first communion.

Frankly, however, the entire procedure all seemed relatively painless to this young child and, in fact, bore many pluses: I got enormous attention from my family and was catapulted from being the youngest and last in the family constellation into the center of the emotional stage.

Three vivid images of the experience remain. The first is when my father was placed on a pallet about twelve inches higher than one I lay on, while we were connected vein to vein so that blood could flow from him to me (presumably because I needed some). It

seemed clear to me at the time that he was directly involved with saving my life. Second is the vision of Dr. Shapiro, the kind pediatric specialist who saw me through the pneumonia and sat head in hand on many evenings observing me for long periods at a time, almost as though he hoped his mere presence would help. (I think it did.) Third was the sense that I have had ever since then, but especially during the next twenty years of my life, that I had escaped death and that I somehow owed something to others. For me, each subsequent birthday and life experience that I celebrate are gifts that would not have been mine to enjoy if all the right people and techniques had not been in the right place at the right time.

Three Physicians View Their Illnesses

Now, more than five decades later, having no real complaint should my life expectancy become somewhat truncated, I might reasonably expect an illness to teach me different lessons and to challenge me in different ways than in my youth. Struggling to make sense of the new experience and almost by serendipity, I stumbled on two records written by physicians, each of whom had also been stricken suddenly with a potentially fatal disease while asymptomatic and happily working away. The first is a brief account by John C. Vander Woude, a young cardiothoracic surgery resident, who was discovered, on routine examination, to have a malignant lymphoma. Because he was about thirty years old and close to the height of his profession, his disease posed a completely different threat to him and his family than the one that I faced. But his experience with the sudden transition from a high-powered operative, controlling the levers of the hospital, to a passive recipient of orders (just as I had encountered) enhanced his understanding (as it did mine) of what the patient goes through at the hands of a health care team and within the sometimes grinding gears of the hospital and overall health care system. For example, as a patient needing his blood drawn at the chemistry lab, he had to wait in line as a supplicant in a setting he used to dominate as a house physician.

Perhaps the most striking description of what a sensitive physician-cum-patient can learn and has to teach the rest of us is in a book by Fitzhugh Mullan. He suddenly discovered via a routine chest x-ray study that he had, much as I had, some unknown, asymptomatic tumor. In Mullan's case, however, the problem was much more severe than mine, the diagnostic process far more complicated and life-threatening, the course in the hospital and treatment to eventual recovery much more prolonged, and the ordeal far more anxiety-producing and trying for his family and his professional life. His story and its lessons are, therefore, that much richer and merit careful review by every caregiver and caregiver-to-be. One vignette from Mullan's story leads nicely into one of the major points that I wish to make from my own experience.

After an extraordinarily grueling, heart-rending struggle with cancer treatment and rehabilitation, Mullan was ready for discharge from the hospital's protective environment to what now seemed to him to be a threatening and strange outside world. He felt, perhaps for the first time, a strong desire to take his own life. Grappling with his feelings, he let the hospital staff know that he needed some help. Shortly, a staff psychiatrist arrived. After listening briefly to the distraught patient, the psychiatrist, in an apparently brilliant therapeutic insight, uttered only seven words, "Do you want me to hold you?" The words turned the entire situation around. The reader of Mullan's work leaves the scene with the vision of two men embracing; one giving of his strength to the other—embattled, scared, and suffering—the power to continue the struggle toward a return of well-being.

This striking story brought home what I had experienced in a less dramatic fashion (two times personally and professionally many times more), namely, the capacity of specialists who do not have frequent or continuing deep encounters with a patient to say or do the right thing at just the right time to hasten the march toward recovery. Over the years, I have encountered some of the reverse as well, but the lesson remains that both the generalist and the specialist have enormous opportunities to influence the course of a patient's treatment, sometimes in ways that flow from professional expertise and sometimes from human nature and personality.

Grateful for the latest breakthroughs. Without embarking on a long (and likely boring) self-analysis, it does seem useful now, as a recent patient, to summarize my impressions of the most important aspects of what I will discuss at length in the next chapters. First and foremost must be the extraordinary scientific and technologic advances now brought to bear on the patient's problems through the professional competence of the modern health care team. That may sound like campaign rhetoric by some apologist for modern American medicine, but it is a heartfelt expression of appreciation from a knowledgeable patient who was surprised at how easy and painless major diagnostic and therapeutic interventions could be. Advances in anesthesia enabled me to go to sleep so quickly and easily, so dimmed any recollection of postoperative pain, and so effectively controlled the anticipated postoperative symptoms that the thoracotomy and other surgical maneuvers are not unpleasant memories and were accomplished within a three- or four-day hospitalization. Surgical techniques (for example, utilizing miniature cameras, reduced incisions, and newly developed professional skills) all served to minimize possible postoperative side effects and make the entire diagnostic phase minimally intrusive and destructive to my remaining strength and resolve to go forward aggressively with necessary chemotherapy.

The science and techniques involved with the chemotherapy itself were most impressive. New medicines successfully prevented the dreaded nausea and vomiting ordinarily associated with the protocol I entered, minimizing the discomfort and trauma of the

repetitive poisoning. Needles used for infusions and the little technologies employed to achieve other routine goals were effective and are continually being improved. Products of our pharmaceutical industry were used to make my bowel habits as nearly normal as possible, to prevent gastrointestinal ulcers from developing, and to manage strange alterations in secretions resulting from the therapy. Although one may argue that we do not need all of those technical advances and that a patient could do without at least some of them, I can categorically state that I remain deeply appreciative for every last one.

Perhaps the most striking technological impact on my own case involved the CT scan of the mediastinum, which uncovered the lesion in the first place and is the best available venue for following the therapy's progress. Without the availability of the scan, my condition would likely have gone undetected for perhaps another year, while the lymphoma grew elsewhere and eventually produced symptoms that would allow for diagnosis by biopsy or other means. Who knows what the difference in outcome would have been if such a delay had occurred? Who knows how high the total cost of my illness could have risen had such a delay been necessary? For my part, I say God bless the CT scan! And God bless the skills and technologies available to most patients in America today! I look forward to the day when everyone has access to these wonders.

Grateful for human support. The second, somewhat surprising finding was my realization of the enormous importance of human support from family, other loved ones, and friends. The cards, letters, telephone calls, thoughts, prayers, and positive sentiments all serve to underscore and encourage the commitment of the patient and family to do whatever is necessary to regain health. I have promised myself that I shall never again be reluctant to extend such support to others for fear of intruding upon a highly personal time. It is, in fact, quite the opposite. Native Americans have long appreciated the value of the tribe's support to the restoration of health; I now understand and appreciate that dimension far more intensely than ever before. In fact, I now realize that some physician colleagues grossly underestimate such support, focusing instead on the science and techniques they know they can apply to a given medical problem.

Retaining dignity. The third lesson that I learned (or relearned) through this illness involves patient empowerment, independence, dignity, and psychological space. If I understand psychiatrist Leston Havens correctly, his therapeutic objective is to create a relationship with his patient in which the two can figuratively coexist and meaningfully interact, but feel no need to invade or be invaded by the other. Implicit in this simple approach is an enormous respect for the dignity and selfhood of the other. Attention to this need is terribly important when patients are physically sick and threatened with dire and dreaded diseases. Being treated with respect by all of the important players during my illness not only helped me to handle the situation, but more important, enabled me to grow as a person. My wife, children, and other relatives all worked to help me act as I thought I should in managing the thousand little daily decisions. My caregivers also were assiduous in attempting to impart the best information and advice that they could, and then encouraging me to make the decisions and to set the course.

Combining this sort of approach with overwhelming support of the group, skills of the professional, and high technology offers the best potential for effective interventions on behalf of the patient. There is no doubt in my mind that the lines begin to blur between the individuals who participate in this network of patient support and the health care institutions through which much of the work is carried out. The interface between individual caregivers and institutions can be highly constructive from the patient's point of view, or it can be quite the opposite. Both extremes occur, as do all of the permutations in between. Identifying and improving those less-than-optimal permutations define the agenda for the health care team and system in the ongoing attempt to provide technically competent and humane care.

The gift of mercy. Finally, I found myself unable to escape Thomas Merton's stylized response to the ritual question of the Trappist order, "What do you ask?" It was, "I ask for the mercy of God and of the Order." Secularizing the answer, it seems to me that, as a patient with a serious, life-threatening illness, I was asking society for mercy in extending to me through its health professionals, its institutions, my family, and loved ones the requisite help to deal with the difficult matters at hand, because I could not do it alone. Whether the helpers be office colleagues or hospital specialists, the sufferer needs their merciful concern and support. At the core must be a latticework of morally accountable, concerned health professionals whose time-honored commitment to the patient's welfare is so central to our system of care.

Therefore, in my opinion, the caregiver's professional essence is based on the sustenance of the principles inherent in the ages-old covenant between doctor (caregiver) and patient: The doctor is the patient's advocate, and the patient's welfare is paramount.

Clearly, in this postmodern world the concept of the solo physician must be extended to include other health-team members. Clearly, too, this foundation is not consistent with a health care system that creates financial incentives for caregivers to serve a corporation's bottom line or their own interests by restricting access to care. In such settings, health professionals are no longer patients' advocates, but advocates of their employers or themselves.

My own illness has underscored my personal commitment to work toward a health care reform that preserves the special therapeutic bond between the professional caregiver and the sufferer, a bond that is central to

the seeking and showing of mercy, one to another! I cannot escape the notion that the extent to which we succeed in maintaining the humanity of our health care system should be an important measure of the quality of our twenty-first century civilization. For me, then, the name of the health care game is, indeed, mercy.

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AMERICAN COLLEGE OF PHYSICIANS . . . . . 2nd Cover

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LANCET . . . . . 4th Cover

CALIFORNIA ACADEMY OF FAMILY PHYSICIANS 313

THE WESTERN JOURNAL OF MEDICINE

The Quest for Mercy Order Form 306

Successful Aging Order Form 314

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VOLUME 167 • NUMBER 6 DECEMBER 1997

ARTICLES

387 Hospital Preparedness for Hazardous Materials Incidents and Treatment of Contaminated Patients
J L BURGESS, G M BLACKMON, C A BRODKIN, and W O ROBERTSON

392 Health Care Professionals' Willingness to Do Mouth-to-Mouth Resuscitation
B Z HOROWITZ and L MATHENY

398 Pulmonary and Allergy Subspecialty Care in Adults With Asthma—Treatment, Use of Services, and Health Outcomes
P D BLANC, P P KATZ, J HENKE, S SMITH, and E H YELIN

COMMENTARIES

408 Respiratory Therapist–Driven Protocols—Rationale and Efficacy
J K STOLLER

411 Withholding and Withdrawal of Life Support From Critically Ill Patients
J M LUCE

417 Mad Cow Disease—An Opportunity for Preventive Medicine?
P SALZMANN, S SAINT, and L M TIERNEY

SPECIAL REPORT

420 The Future of Veterans Affairs Medical Centers
C B SMITH

EPITOMES

426 Important Advances in Otolaryngology

ALERTS, NOTICES, AND CASE REPORTS

430 Severe Hypernatremia From Sea Water Ingestion During Near-Drowning in a Hurricane
R J ELLIS

433 Long-Term Remission of HIV-Associated Thrombocytopenia Parallels Ongoing Suppression of Viral Replication
S C ZELL and K PETERSON

435 Reversible Muscle Weakness in Patients With Vitamin D Deficiency
K ZIAMBARAS and S DAGOGO-JACK

EDITORIAL

440 Respiratory Therapist–Driven Protocols
L ZIMMERMAN

SPECIAL SERIES—PART I

442 A Few Words About *The Quest for Mercy*
L H CLEVER

443 The Quest for Mercy—The Forgotten Ingredient in Health Care Reform
R BULGER

OTHER FEATURES

386 Subscription Information
457 1997 Reviewer list
458 Volume Index
381 Continuing Medical Education Activities
462 Classified Advertising

Detailed Table of Contents: 379, 380

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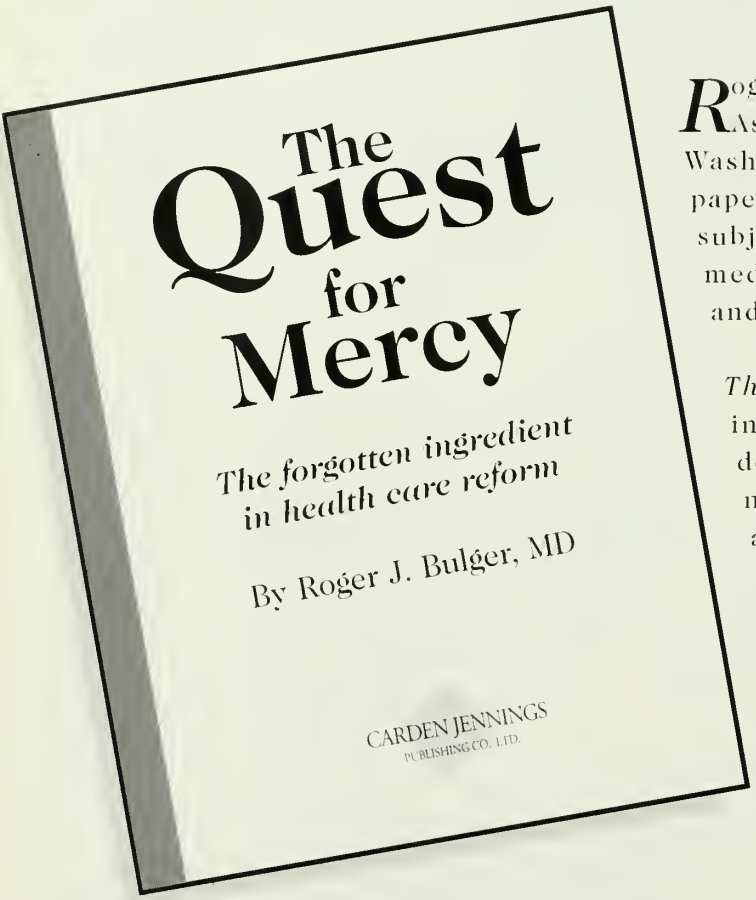

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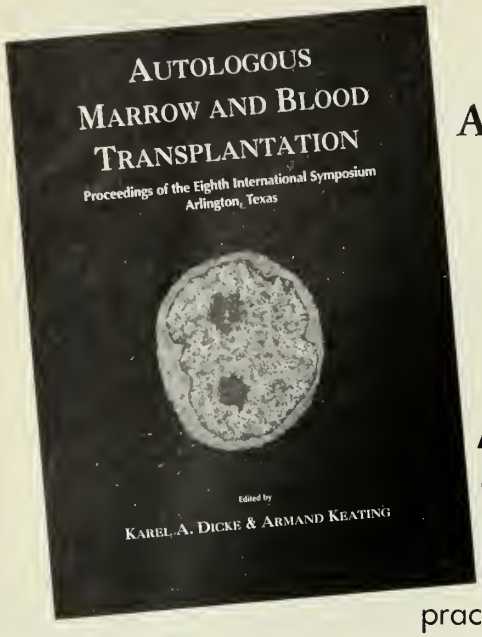

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CONTENTS

ARTICLES

387 **Hospital Preparedness for Hazardous Materials Incidents and Treatment of Contaminated Patients**

JEFFEREY L. BURGESS, MD, MS, MPH; GRIFFITH M. BLACKMON, MD, MPH; C. ANDREW BRODKIN, MD, MPH; *and* WILLIAM O. ROBERTSON, MD

From the Division of Infectious Diseases and Geographic Medicine, Stanford University Medical Center, Stanford; Department of Pharmacology, Chiang Mai University, Chiang Mai, Thailand; and Department of Medicine, University of California, San Francisco, and the Medical Service, San Francisco General Hospital and Medical Center.

392 **Health Care Professionals' Willingness to Do Mouth-to-Mouth Resuscitation**

B. ZANE HOROWITZ, MD, *and* LEONA MATHENY, RN, MN

From the Division of Emergency Medicine and the Center for Continuing Nursing and Medical Education, University of California, Davis, Medical Center, Sacramento; and the Oregon Poison Center, Oregon Health Sciences University, Portland.

398 **Pulmonary and Allergy Subspecialty Care in Adults With Asthma—Treatment, Use of Services, and Health Outcomes**

PAUL D. BLANC, MD, MSPH; PATRICIA P. KATZ, PhD; JONATHAN HENKE; SHERMAN SMITH; and EDWARD H. YELIN, PhD

From the Division of Occupational and Environmental Medicine, the Arthritis Research Group, Department of Medicine, and the Institute for Health Policy Studies, University of California, San Francisco, School of Medicine.

COMMENTARIES

408 **Respiratory Therapist–Driven Protocols—Rationale and Efficacy**

JAMES K. STOLLER, MD

From the Section of Respiratory Therapy, Cleveland Clinic Foundation, Department of Pulmonary and Critical Care Medicine, Cleveland, Ohio.

411 **Withholding and Withdrawal of Life Support From Critically Ill Patients**

JOHN M. LUCE, MD

From the Departments of Medicine and Anesthesia, University of California, San Francisco, and the Medical-Surgical Intensive Care Unit, San Francisco General Hospital and Medical Center.

417 **Mad Cow Disease—An Opportunity for Preventive Medicine?**

PETER SALZMANN, MD; SANJAY SAINT, MD; *and* LAWRENCE M. TIERNEY Jr, MD

From the Department of Medicine, San Francisco Veterans Affairs Medical Center, and University of California, San Francisco, School of Medicine; and the Robert Wood Johnson Clinical Scholars Program, University of Washington School of Medicine, Seattle.

SPECIAL REPORT

420 **The Future of Veterans Affairs Medical Centers**

CHARLES B. SMITH, MD

From the Department of Medicine, University of Washington School of Medicine, and the Veterans Affairs (VA) Puget Sound Health Care System, Seattle, Washington.

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Otolaryngology

Items of progress in otolaryngology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance.

426 **Sleep Studies and Primary Care**

TERENCE M. DAVIDSON, MD

(Continued from Page 379)

426 **Vocal Cord Paralysis**
LISA A. ORLOFF, MD

427 **Removing Double Chins—The Role of Submentoplasty**
RICHARD L. GOODE, MD

428 **An Overview of Facial Wrinkles**
R. JAMES KOCH, MD

ALERTS, NOTICES, AND CASE REPORTS

430 **Severe Hypernatremia From Sea Water Ingestion During Near-Drowning in a Hurricane**
ROBERT J. ELLIS, MD
From the Department of Internal Medicine, U.S. Naval Hospital Roosevelt Roads, Puerto Rico.

433 **Long-Term Remission of HIV-Associated Thrombocytopenia Parallels Ongoing Suppression of Viral Replication**
STEVEN C. ZELL, MD, and KEVIN PETERSON, MD
From the Department of Internal Medicine, University of Nevada School of Medicine, and the Washoe Medical Center, Reno.

435 **Reversible Muscle Weakness in Patients With Vitamin D Deficiency**
KONSTANTINOS ZIAMBARAS, MD, and SAMUEL DAGOGO-JACK, MD
From the Division of Endocrinology, Diabetes, and Metabolism, Washington University School of Medicine, St Louis, Missouri.

EDITORIAL

440 **Respiratory Therapist–Driven Protocols**
LESLIE ZIMMERMAN, MD
From the Division of Pulmonary/Critical Care Medicine, University of California, San Francisco, School of Medicine.

Special Series

442 **A Few Words About *The Quest for Mercy***
LINDA HAWES CLEVER, MD

443 **Part II—The Quest for Mercy—The Forgotten Ingredient in Health Care Reform**
ROGER J. BULGER, MD

OTHER FEATURES

386 Subscription Information
457 1997 Reviewer list
458 Volume Index
381 Continuing Medical Education Activities
462 Classified Advertising

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

Continuing Medical Education

ARIZONA • CALIFORNIA, HAWAII, NEVADA • COLORADO • IDAHO • NEW MEXICO • UTAH • WASHINGTON • WYOMING

ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd. Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (520) 626-7832; (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Paulette Richardson, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-3387. For more information on accreditation or certification, please write to the above address.

ALLERGY

January 18–23, 1998—**36th Annual Scientific Session of The Western Society of Allergy and Immunology.** Four Seasons Resort, Wailea in Maui, Hawaii. For more information contact Rebecca Gough, Exec. Administrator, PO Box 1122, Roanoke, Texas, 76262; (817) 491-2616, Fax (817) 491-2241.

ANESTHESIOLOGY

January 7–10, 1998—**UCSD Anesthesiology Update 1998.** UCSD at Hotel del Coronado, San Diego. Wed.–Sat. 18 hrs. Contact: Carol Heil (619) 543-2188.

May 17–22, 1998—**UCSD Anesthesiology Review Course.** UCSD at La Jolla Marriott, San Diego. Sun.–Fri. 37.5 hrs. $600. Contact: Carol Heil (619) 543-5202.

CARDIOLOGY

January 16–17, 1998—**Radiotherapy to Reduce Restenosis.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri.–Sat. 16.5 hrs. Contact: Laurel Steigerwald, Scripps Clinic Dept. Academic Affairs 403c, 10666 N. Torrey Pines Road, La Jolla 92037. (619) 554-8556.

January 24, 1998—**Heart Failure.** Ritz-Carlton Huntington Hotel, Pasadena. Sat. 5 hrs. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles, 90033-1039. (800) USC-1119, fax (213) 342-2152.

January 30–February 1, 1998—**Clinical Nuclear Cardiology: Case Review With the Experts.** American College of Cardiology at Cedars-Sinai Medical Center, Los Angeles. Fri.–Sun. 19 hrs. Contact: ACC Registration Secretary, Extramural Programs Dept., (800) 253-4636, ext. 695.

February 19–21, 1998—**Cardiovascular Health: Coming Together for the 21st Century.** UCSF at Hyatt Regency Embarcadero San Francisco. Thurs.–Sat. Contact: UCSF.

May 7–9, 1998—**8th Annual Symposium on Coronary Stenting.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs.–Sat. Contact: Laurel Steigerwald, Scripps Clinic (619) 554-8556.

COMPUTER TECHNOLOGY

January 28–31, 1998—**Medicine Meets Virtual Reality: Art, Science, Healthcare Evolution.** UCSD at San Diego Hyatt Regency. Wed.–Sat. Contact: Karen Morgan (760) 751-8841.

DERMATOLOGY

January 15–18, 1998—**Practical Dermatology for the Primary Care Physician.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency La Jolla, San Diego. Method, AV, L, SB, W. $575. Thurs.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

January 31–February 1—**Melanoma 1998: 8th Annual Cutaneous Malignancy Update.** Scripps Clinic at Scripps Memorial Hospital, La Jolla. Sat.–Sun. 11.5 hrs. Contact: Jill Hofmans, Scripps Clinic, (619) 554-8556.

May 3–6, 1998—**Practical Dermatology for the Primary Care Physician.** Las Vegas. Sponsored by Continuing Medical Education Associates. Caesar's Palace Las Vegas. Method, AV, L, SB, W. $575. Sun.–Wed. 20 hrs. credit: AMA, AOA, AAP, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

EMERGENCY MEDICINE

February 27–March 3, 1998—**Critical Care Medicine.** Las Vegas Hilton Hotel, Las Vegas. Fri.–Tues. 26 hrs. Cost: $785/MD, $585/Allied Health. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

February 16–20, 1998—**Emergency Medicine Symposium I.** UCSD at La Jolla Marriott San Diego. $495. Mon.–Fri. 32 hrs. Contact: OCME (619) 534-3940.

March 25–27, 1998—**14th Annual Advances in Emergency Medicine.** UCSF at Radisson Miyako Hotel, San Francisco. Wed.–Fri. 17 hrs. $520. Contact: UCSF (415)476-5208.

April 20–24, 1998—**Emergency Medicine Symposium III.** UCSD at La Jolla Marriott, San Diego. Mon.–Fri. 32 hrs. $495. Contact: OCME (619) 534-3940.

May 11–15, 1998—**Emergency Medicine Symposium.** UCSD at La Jolla Marriott, San Diego. Mon.–Fri. 16 hrs. $225. Contact: OCME (619) 534-3940.

May 15–16, 1998—**Trauma/Critical Care.** Ritz-Carlton Huntington Hotel, Pasadena. Mon.–Tues. 14 hrs. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

May 13–16—**Semiannual Wound Management Workshop.** UCSD at La Jolla Marriott, San Diego. Wed.–Sat. 15 hrs. $475. Contact: Edith Bookstein (619) 454-3212.

ENDOCRINOLOGY

March 5, 1998—**Diabetes Update.** UCSF at Radisson Miyako Hotel, San Francisco. Thurs. 7.5 hrs. $195. Contact: UCSF (415)476-5208.

March 6–7, 1998—**Advances in Endocrinology and Metabolism.** UCSF at Radisson Miyako Hotel, San Francisco. Fri.–Sat. 11 hrs. $310. Contact: UCSF (415)476-5208.

FAMILY PRACTICE/PRIMARY CARE

January 15–18, 1998—**Practical Dermatology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Regency, La Jolla. Thurs.–Sun. 20 hrs. $575. Contact: Victoria Gonzales (800)993-2632.

April 9–10, 1998—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** Stanford Court Hotel, San Francisco. 14 hrs. $375 ($425 if postmarked after February 26). Contact: Program Coordinator, Dept. of Family and Community Medicine, UCSF School of Medicine, 500 Parnassus Ave., MU-3E, San Francisco 94143-0900. (415) 476-5250.

February 5–6, 1998—**Clinical Allergy and Immunology for Primary Care Family Physicians.** UCSF at Radisson Miyako Hotel, San Francisco. Thurs.–Fri. 7.5 hrs. $125. Contact: UCSF (415)476-5208.

February 12–15, 1998—**Office Gynecology and Women's Health for the Primary Care Physician.** UCSF at Hyatt Islandia, San Diego. Thurs.–Sun. 20 hrs. $575. Contact: Victoria Gonzales (800)993-2632.

March 14, 1998—**Gastroenterology and Hematology Update for the Primary Care Physician and Hands-On Flexible Sigmoidoscopy Workshop.** UC Davis at Cancer Center Auditorium, Sacramento. Sat. 6 hrs. $105. Contact: UCD (917)734-5390.

April 18, 1998—**Cardiology for the Primary Care Physician.** UC Davis at UCDMC Cancer Center Auditorium, Sacramento. Sat. Contact: (916) 734-7203.

April 23–26, 1998—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Regency, San Francisco. Thurs.–Sun. 20 hrs. $575. Contact: Victoria Gonzales (800) 993-2632.

May 15–19, 1998—**Primary Care Essentials.** San Francisco. Sponsored by Continuing Medical Education Associates. Grand Hyatt on Union Square San Francisco. Method, AV, L, SB, W. $750. Fri.–Tues. 32 hrs. credit: AMA, AOA, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

July 6–9, 1998—**Family Practice Board Review Course.** Fairmont Hotel, San Francisco. 25 hrs. $475 ($525 if postmarked after May 25). Contact: Program Coordinator, Dept. of Family and Community Medicine, UCSF School of Medicine, 500 Parnassus Ave., MU-3E, San Francisco 94143-0900. (415) 476-5250.

GERIATRICS

May 7–8, 1998—**Latest Advances in Alzheimer's Disease.** UCSD at San Diego. Thurs.–Fri. 16 hrs. $225. Contact: Phyllis Lessin/Joyce Zilner (619) 662-5800.

INFECTIOUS DISEASE

February 6–7, 1998—**16th Annual Infectious Disease Conference.** UC Davis Medical Center at Sacramento Hilton Inn. Fri.–Sat. Contact: (917) 734-5390.

February 19–21, 1998—**Epidemiology and Prevention of Infectious Diseases.** UCSF at Grand Hyatt on Union Square, San Francisco. Thurs.–Sat. Contact: UCSF (415) 476-5208.

May 6–9, 1998—**19th Annual Advances in Infectious Diseases.** UCSF at Palace Hotel, San Francisco. Wed.–Sat. 17.5 hrs. $430. Contact: UCSF (415) 476-5208.

INTERNAL MEDICINE

March 7–14, 1998—**Diagnostic & Therapeutic Skills in Internal Medicine.** Mauna Kea Beach Hotel, Kameula, HI. Mon.–Fri. 27 hrs. $635. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119. fax (213) 342-2152.

March 20–26, 1998—**Internal Medicine 1998.** San Diego. Sponsored by Continuing Medical Education Associates. Hotel del Coronado San Diego. Method, AV, L, SB, W. $795. Fri.–Thurs. 45 hrs. credit: AMA, AOA, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

April 2–5, 1998—**1998 Annual Session American College of Physicians.** ACP at San Diego Convention Center. Wed.–Sun. 29 hrs. Contact: ACP Customer Service (800) 523-1546 ext. 2600.

April 4, 1998—**New Treatments in Chronic Liver Disease.** Scripps Clinic at Scripps Clinic, La Jolla. Fri 6 hrs. Contact: Laurie A. Regis (619) 554-8556.

May 18–22, 1998—**26th Annual Advances in Internal Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon.–Thurs. 33.5 hrs. Contact: UCSF (415) 476-5208.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Education Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education, (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

NEPHROLOGY

January 29–31, 1998—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at La Jolla Marriott. Thurs.–Sat. 17 hrs. $425.

NEUROLOGY

January 31, 1998—**UCLA Neurology: Update for Primary Care Physicians.** Miramar Sheraton Hotel Santa Monica. 6 hrs. Contact: Sheryl Crowley, Office of Continuing Medical Education, 10920 Wilshire Blvd., Los Angeles 90024-6512 (310) 794-2620; Fax (310) 794-2624..

February 11–13, 1998—**Recent Advances in Neurology.** UCSF at Fairmont Hotel San Francisco. Wed.–Fri. 15 hrs. Contact: UCSF (415) 476-4251.

March 20, 1998—**STROKE: Van Der Meulen Symposium in Clinical Science.** USC Health Sciences Campus, Los Angeles. Fri. 7 hrs. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

NEUROSURGERY

January 16–18, 1998—**California Association of Neurological Surgeons Annual Session.** Parc Fifty Five Hotel, San Francisco. 7 hrs. Contact: Janine Tash, 5380 Elvas Ave., Ste. 216, Sacramento 95819, (916) 457-2267, fax (916) 457-8202.

OB/GYN

February 14–20, 1998—**Perinatal Medicine.** Westin Maui Hotel, Maui, HI. Mon.–Thur. 20 hrs. $625. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

February 12–15, 1998—**Office Gynecology and Women's Health for the Primary Care Physician.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Islandia San Diego. Method, AV, L, SB, W. $575. Thurs.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 28–March 3, 1998—**15th Annual OB/GYN Update: 1998.** UC Davis Medical Center at Harrah's Lake Tahoe Casino/Resort, South Lake Tahoe. Sat.–Tues. 16 hrs. credit. Contact: (916) 734-5390.

OCCUPATIONAL & ENVIRONMENTAL

March 6–7, 1998—**Mental Health Litigation and the Workplace.** UC Davis at Silverado Country Club and Resort, Napa. 10 hrs. $199. Contact: UCD (916) 734-1394.

March 30–April 3, 1998—**Occupational & Environmental Medicine V.** UCSF at Radisson Miyako Hotel, San Francisco. Sun.–Thurs. 40 hrs. $750. Contact: UCSF (415) 476-5208.

May 15–16, 1998—**17th Annual Occupational & Environmental Medicine Symposium with Postgraduate Mini-Courses.** UC Davis at UCDMC Cancer Center Auditorium, Sacramento. Thurs.–Fri. Contact: UCD (916) 734-1394.

ONCOLOGY

January 16–17, 1998—**Radiotherapy to Reduce Restenosis.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri.–Sat. 16.5 hrs. Contact: Laurel Steigerwald, Scripps Clinic Dept. Academic Affairs 403c, 10666 N. Torrey Pines Road, La Jolla, 92037 (619) 554-8556.

January 29–31, 1998—**Hematology and Oncology: Current Concepts and**

Controversies. UCSF at Radisson Miyako Hotel, San Francisco. Thurs.–Sat. $395. Contact: UCSF (415) 476-5208.

February 16–19, 1998—**Clinical Hematology & Oncology.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel La Jolla. Fri.–Mon. 24 hrs. Contact: Laurie A. Regis, Scripps Clinic (619) 554-8556.

OPHTHALMOLOGY

May 9, 1998—**Pearls of Ocular Therapy.** Scripps Clinic at Scripps Clinic, La Jolla. Sat. 7 hrs. Contact: Laurie A. Regis, Scripps Clinic (619) 554-8556.

May 29, 1998—**UC Davis Annual Ophthalmology Symposium.** UCD at Sacramento Hilton. Fri. 7 hrs. Contact: UCD (916) 734-1394.

ORTHOPEDICS

April 23–26, 1998—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency San Francisco. Method, AV, L, SB, W. $575. Thurs.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

May 3–6, 1998—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Las Vegas. Sponsored by Continuing Medical Education Associates. Caesar's Palace Las Vegas. Method, AV, L, SB, W. $575. Sun.–Wed. 20 hrs. credit: AMA, AOA, AAP, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

PEDIATRICS

January 24, 1998—**Update in Behavioral/Developmental Pediatrics.** UCSF at campus of UCSF. Sat. Contact: UCSF.

February 6–11, 1998—**PREP the Course.** AAP at Fairmont Hotel San Francisco. Fri.–Wed. 44 hrs. Contact: AAP (800) 433-9016, ext. 6796 or 7657.

February 15–18, 1998—**Pediatrics Update 1998.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Islandia San Diego. Method, AV, L, SB, W. $575. Sun.–Wed. 20 hrs. credit: AMA, AOA, AAP, AAFP. Information: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 16–19, 1998—**Clinical Hematology and Oncology: 1998.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel La Jolla. Fri.–Mon. 24 hrs. Contact: Laurie A. Regis, Scripps Clinic (619) 554-8556.

May 7–9, 1998—**31st Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs.–Sat. Contact: OCME (415) 476-4251.

PSYCHOLOGY

March 28, 1998—**Advanced Psychopharmacology for Clinicians: Practical Strategies for Management and Treatment of Refractory Schizophrenia, Bipolar Disorder and Depression.** UC Davis at Cancer Center Auditorium, Sacramento. Sat. 4hrs. $60. Contact: UCD (917) 734-5390.

RADIOLOGY

January 16–17, 1998—**Radiotherapy to Reduce Restenosis.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri.–Sat. 16.5 hrs. Contact: Laurel Steigerwald, Scripps Clinic Dept. Academic Affairs 403c, 10666 N. Torrey Pines Road, La Jolla, 92037 (619) 554-8556.

April 17–19, 1998—**4th Annual Breast Imaging and Interventions.** UCSD at San Diego Hilton. Fri–Sun. 20 hrs. $350. Contact: OCME (619) 534-3940.

SURGERY

January 9–10, 1998—**What's New in General Surgery: 20th Annual Postgraduate Course.** UC Davis at Hyatt Regency Sacramento. Fri.–Sat. 12.75 hrs. $280. Contact: UCD (916) 734-5390.

April 16–18, 1998—**Recent Advances in Stem Cell Transplantation.** UCSD at San Diego Hilton. Thurs.–Sat. 20 hrs. $350. Contact: OCME (619) 534-3940.

April 16–18, 1998—**Techniques in Arthritis Surgery.** Ritz-Carlton Huntington Hotel, Pasadena. Wed.–Sat. 24 hrs. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

May 9, 1998—**Thyroid Update '98.** Sheraton Grande Hotel, Los Angeles. Sat. 7 hrs. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

UROLOGY

April 23–25, 1998—**International Bladder Research Congress.** UCSF at San Francisco. Thurs.–Sat. 17.5 hrs. $290–$395. Contact: (415) 476-5808.

GENERAL/MULTIDISCIPLINARY

January 28–31, 1998—**Medicine Meets Virtual Reality: Art, Science, Technology: Healthcare (R)Evolution.** San Diego Hyatt Regency. Wed.–Sat. Contact: AMA, Inc. (760) 741-8841.

January 31–February 2, 1998—**Spanish for the Medical Profession.** San Diego. Maricopa Health System. $695. 36 hrs. Contact: Joanna Rios, 1351 E. Ft. Lowell Road, Suite C, Tucson, AZ 85719. (619) 218-4875 or (520) 881-3295.

February 13–16, 1998—**California Academy of Family Physicians 50th Annual Scientific Assembly.** Anaheim Hilton and Towers. $275–$385. 26+ hrs. Contact: Clark W. Franklin, California Academy of Family Physicians, 114 Sansome St., Suite 1305, San Francisco, CA 94104-3824. (415) 394-9121; fax (415) 394-9119; Email: cfranklin@familydocs.org.

February 25–March 1, 1998—**7th Annual Winter Board Review for Physician Assistants.** Holiday Inn, Pasadena. Wed.–Sun. 30 hrs. $345; $245 student rate. Contact: USC School of Medicine, Postgraduate Div., 1975 Zonal Ave., KAM 307, Los Angeles 90033-1039. (800) USC-1119, fax (213) 342-2152.

HOME STUDY/SELF-ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Second Wednesday of Each Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

The listing of continuing medical education programs in Idaho is compiled by the Ada County Medical Society. To list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701. (208) 336-2930.

Brochures, course information, and registration forms are available from the contact person or organization.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

January 23–24, 1998—**28th Annual Winter Pediatric Orthopaedic Seminar.** Albuquerque. Fri.-Wed. Contact: UNM Continuing Medical Education, Campus Box 713, Albuquerque, NM 87131-5126. (505) 272-3942, fax (505) 272-8604.

January 24–25, 1998—**16th Annual Albuquerque Family Practice Seminar.** Radisson Hotel Carlisle at I-40, Albuquerque. Sponsor: New Mexico Academy of Family Physicians. Contact: Ann Woodrow, (505) 243-4560..

February 25–28, 1998—**Advances in Neurology.** Santa Fe. Contact: UNM Continuing Medical Education, Health Sciences and Services Building, Room 140, Box 713, Albuquerque, NM 87131-5126. (505) 272-3942, fax (505) 272-8604 or e-mail dmurray@unm.edu..

March 20–21, 1998—**Advances in Primary Care.** Albuquerque. Crowne Plaza Hotel. Contact: UNM Continuing Medical Education, Campus Box 713, Albuquerque, NM 87131-5126. (505) 272-3942, fax (505) 272-8604.

SATELLITE COURSES

Contact: Joe Treat or Jim Cato, Immunization Program, (505) 827-2366

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

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Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

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AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. June 26–28, 1998—**Fortieth Annual Scientific Meeting of The American Association for the Study of Headache.** Sheraton Palace, San Francisco. Contact: (609) 845-1720

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. November 6–8, 1998—**Scottsdale Headache Symposium.** Scottsdale at Marriott's Camelback Inn Resort & Spa. Contact: (609) 845-1720..

AMERICAN COLLEGE OF CARDIOLOGY. Feburary 11–14, 1998—**Cardiovascular Conference at Snowbird.** Cliff Lodge, Snowbird, UT. 18.5 hrs. Contact: Registration Secretary, Extramural Programs Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814-1699. (800) 253-4636, ext. 695 (outside U.S. and Canada, 301-897-5400, ext. 695); FAX (301) 897-9745.

AMERICAN COLLEGE OF MEDICAL GENETICS. February 27–March 1, 1998—**5th Annual Meeting & 29th Annual March of Dimes Clinical Genetics Conference.** Bethesda, Md. Up to 17.5 hrs. Contact: ACMG, 9650 Rockville Pike, Bethesda, MD 20814. (301) 530-7127; Fax (301) 571-1895; E-mail, mgross@genetics.faseb.org.

AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE. April 24–May 1, 1998—**57th American Occupational Health Conference.** Boston, Mass. Contact: ACOEM, 55 W. Seegers Rd., Arlington Heights, Ill 60005. (847) 228-6850, ext. 184, FAX (847) 228-1856; Website: www.acoem.org.

AMERICAN DIABETES ASSOCIATION. March 27–29, 1998—**Type 2 Diabetes in the Elderly.** The Buttes Resort Tempe (Phoenix), Az. Contact: FAX (602) 861-0542.

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the University of Arizona Health Sciences Center Dept. of Pathology, and endorsed by the American Thoracic Society.25.75 hours. $745 before Nov. 26; $795 after. Contact: Armed Forces Institute of Pathology, Center for Advanced Medical Education, Washington, DC 20306-6000. (800) 577-3749; URL: http://www.afip.mil/courses.

The Atopy Syndrome in the Third Millenium. *October 2–3, 1998,* Zurich, Switzerland, on the occasion of the 50th anniversary of the allergy unit at the Dept of Dermatology, University Hospital, Zurich, and in collaboration with the European Academy of Allergology and Clinical Immunology. Contact: Prof. Dr. B. Wüthrich, Zurich, 41-1-255-3079, fax 41-1-255-4431.

The Fifth Annual Alimentary Update 1998. *February 19, 20, & 21, 1998,* Harveys Resort Hotel/Casino at Lake Tahoe, Nv. Contact: (702) 328-4964; Fax (702) 328-4540; email whsinfo@washoehealth.com.

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WJM10

Articles

Hospital Preparedness for Hazardous Materials Incidents and Treatment of Contaminated Patients

JEFFEREY L. BURGESS, MD, MS, MPH; GRIFFITH M. BLACKMON, MD, MPH; C. ANDREW BRODKIN, MD, MPH; *and* WILLIAM O. ROBERTSON, MD, *Seattle, Washington*

Hospital-based facilities providing emergency care in the state of Washington were surveyed to determine their level of preparedness for hazardous materials incidents including the treatment of contaminated patients. Responses to a faxed questionnaire were received from 95 (94%) of the 101 emergency care facilities in Washington State. Only 42 (44%) of the facilities reported the ability to receive any chemically exposed patient. Of the 95 responding emergency care facilities, 39 (41%) had no designated decontamination facilities; 67 (70%) had protocols for handling chemical contamination and possible evacuation from hazardous materials spills, and 52 (55%) had protocols for handling medical facility contamination and possible evacuation from treating chemically contaminated patients. Twelve (13%) facilities had evacuated their emergency department or other part of the hospital for contamination incidents in the past 5 years. Despite the frequent occurrence of hazardous materials incidents, most emergency care facilities in Washington State are not fully prepared to handle contaminated patients and chemical spills. This may have important implications for the care of persons with exposure to hazardous materials and for implementing Joint Commission on Accreditation of Healthcare Organizations standards and federal Occupational Safety and Health Administration regulations.

(Burgess JL, Blackmon GM, Brodkin CA, Robertson WO. Hospital preparedness for hazardous materials incidents and treatment of contaminated patients. West J Med 1997; 167:387–391)

Hazardous materials incidents occur frequently on a regional basis. In the state of Washington from 1992 through 1994, there were 1,444 hazardous materials incidents reported to the state Department of Health, including 333 incidents involving human exposures with 1,268 exposure victims.[1] A hazardous material may be defined as a substance capable of creating harm to people, property, and the environment,[2] and hazardous materials incidents include airborne releases of gas and vapor, spills of solid and liquid material, and explosions and fires resulting in chemical release to the environment. Victims of exposure to hazardous materials are often transported by ambulance to a single designated medical facility for treatment. In many incidents, however, and especially following large-scale exposures, patients are transported to a number of different facilities. Patients also arrive unannounced at medical facilities, without previous decontamination, after substantial hazardous materials exposure. Emergency care facilities may thus encounter a wide variety of hazardous materials exposures with little warning and only limited information about the extent of exposure.

The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) requires accredited institutions to have "emergency procedures that describe the specific precautions, procedures, and protective equipment used during hazardous materials and waste spills or exposures." The JCAHO standards also include "a management plan [that] addresses emergency preparedness," including "evacuating the facility when the environment cannot support adequate patient care and treatment" and "facilities for radioactive or chemical isolation and decontamination."[3] For emergency response and hazardous waste operations, the Occupational Safety and Health Administration requires a site-specific safety and health plan, including an emer-

From the Occupational and Environmental Medicine Program, Department of Medicine, University of Washington School of Medicine (Drs Burgess, Blackmon, and Brodkin), and the Washington Poison Center (Drs Burgess and Robertson), Seattle.

Reprint requests to Jefferey L. Burgess, MD, MS, MPH, Occupational and Environmental Medicine Program, Harborview Medical Center, 325 Ninth Ave, Box 359739, Seattle, WA 98104.

1. Does your hospital have the ability to receive patients who have been exposed to hazardous chemical materials?
   a) any exposed patients Yes___ No___
   b) only patients decontaminated before arrival Yes___ No___
   c) patients exposed to radioactive materials Yes___ No___
   d) other (please describe)
2. What facilities for decontamination do you have available?
   a) area with separate ventilation and water containment Yes___ No___
   b) area with separate ventilation only Yes___ No___
   c) portable (outside) decontamination unit Yes___ No___
   d) none Yes___ No___
   e) other (please describe)
3. How many times have you used your chemical decontamination facilities within the past 12 months? N/A___ 0___ 1–5___ 6–10___ >10___
4. Have you evacuated your emergency department or other parts of the hospital due to a hazardous materials exposure during the past five (5) years? Yes___ No___
5. Do you have a protocol for handling hazardous chemical contamination and possible evacuation of your emergency department or other areas of the hospital?
   a) for hazardous materials spills Yes___ No___
   b) for contaminated patients Yes___ No___
6. Do you have a written protocol for treatment of patients exposed to hazardous materials? Yes___ No___

Figure 1.—This hospital survey questionnaire was sent to 101 Washington State emergency care facilities.

gency response plan that includes identifying the nearest medical assistance. The emergency response plan also requires pre-emergency planning for emergency medical treatment and first aid.[4] Unfortunately, actual emergency response plans frequently designate hospitals for provisional emergency medical treatment without assessing the hospitals' ability to provide care to chemically contaminated patients.

Two recent hazardous materials incidents in Washington State that resulted in emergency department closure focused our attention on hospital preparedness for managing chemical contamination. In the first incident, a patient contaminated from an explosion at a clandestine methamphetamine laboratory presented at a local hospital without previous decontamination. Shortly after his arrival, headache, nausea, vomiting, and mucous membrane irritation developed in several of the hospital staff. The emergency department was closed for seven to eight hours while the situation was assessed and the facility was decontaminated.[5(p7)] In the second incident, another emergency department was temporarily closed when similar adverse symptoms developed among hospital staff treating a patient with occupational chemical exposure. The facility was reopened after evaluation by an outside hazardous materials team. To assess overall preparedness for such chemical exposure incidents, we conducted a survey of all 101 hospital-based emergency care facilities in Washington State.

Methods

Facilities providing emergency care in Washington State were identified through the Washington Poison Center, the Washington State Medical Association, and the American Hospital Association.[6] Of the 120 hospitals and affiliated health care institutions in the state, 101 emergency care facilities were identified. A one-page questionnaire was sent by facsimile machine to all 101 emergency care facilities in June 1996. For facilities not responding within a month, a second questionnaire was sent by facsimile. All facilities not responding to the second questionnaire were contacted by phone to obtain a specific contact person, and a third questionnaire was sent. Incomplete or ambiguous answers were clarified through a telephone interview by one of us (J.L.B.).

The survey questionnaire (Figure 1) consisted of identifying information and a limited set of questions designed to ascertain each institution's self-assessed capability, including physical facilities and existing policies, to care for persons contaminated with hazardous materials. Based on JCAHO standards and our experience with chemical exposures in Washington State, adequate preparation for hazardous materials incidents was considered to include the following:

- Facilities for radioactive or chemical isolation and decontamination;
- A plan for evacuating the facility for sources of contamination, including spills or contaminated patients, or both; and
- A written protocol for the treatment of patients exposed to hazardous materials.

Information on hospital size, as determined by bed count, was collected from *The American Hospital Association Guide to the Health Care Field*.[6] Washington State population data by county were collected from the current world almanac.[7(p444)] Statistics on

TABLE 1.—*Self-Assessed Hospital (n = 95) Ability to Receive Exposed Patients*

Hospital Ability to Receive Patients	*Hospitals, No. (%)*
Any exposed patients	42 (44)
Only patients decontaminated before arrival	47 (49)
Patients exposed to radioactive materials*	28 (29)
Not able to receive exposed patients	6 (6)

*Not mutually exclusive with other categories.

TABLE 2.—*Self-Assessed Hospital (n = 95) Decontamination Facilities*

Facility	*Hospitals, No. (%)*
Separate ventilation and water containment	22 (23)
Separate ventilation only	13 (14)
Portable (outside) decontamination*	23 (24)
Other†	8 (8)
None‡	39 (41)

*Not mutually exclusive with other categories.
†Other decontamination facilities included a special gurney and floor cloths (meeting naval requirements), designated rooms with shower without separate ventilation or water containment, and an outside shower.
‡An outside hose was not counted as a designated decontamination facility unless a continuous source of warm water was available.

the number of hazardous materials incidents, number of incidents involving human exposure, and the total number of chemical exposure victims for each county in Washington State were collected from the Washington State Department of Health.[1] Analyses were performed using SPSS software (SPSS for Windows 6.1, SPSS Inc, Chicago, Illinois) to determine the association of hospital size (by bed count) with elements of hospital preparedness and to determine the correlation of county population with the number of hazardous materials events, hazardous materials victim events, and hazardous materials exposure victims by county. Odds ratios (OR) were calculated using standard 2×2 contingency tables, with 95% confidence intervals (CI) .

Results

Questionnaires were sent by facsimile machine to all 101 designated emergency care facilities in the state of Washington. A total of 95 (94%) were returned. The person completing the questionnaire varied by facility: 67 (71%) respondents were registered nurses with administrative positions, including director of nursing services, emergency department director, clinical services manager, or risk manager; 9 (9%) were physician emergency department directors or assistant directors; and 14 (15%) were safety, engineering, operations, or other personnel without an MD or RN degree. The remaining five (5%) respondents were nonadministrative staff nurses or physicians.

The number of inpatient beds associated with the designated emergency facilities ranged from 0 to 686, with a median of 74 beds. Of the 95 emergency facilities, 92 were physically located in hospitals. Three emergency care facilities had no inpatient beds but transferred patients requiring admission to nearby inpatient treatment facilities. The self-assessed ability of Washington State emergency care facilities to receive patients with exposure to hazardous materials is presented in Table 1. The self-assessed availability of designated decontamination facilities is presented in Table 2. Of the 56 emergency care centers with decontamination facilities, 45 (80%) had not used their facilities for decontamination during the previous 12 months, and 11 (20%) had used their facilities less than five times. No facility had been used more than five times during the previous 12 months.

For hazardous materials spills, 67 (70%) emergency care facilities had a protocol for handling hazardous chemical contamination and evacuation of their department or other areas of the hospital. For the treatment of contaminated patients, 52 (55%) emergency care facilities had a protocol for handling hazardous chemical contamination and evacuation of their department or other areas of the hospital. In all, 49 (52%) emergency care facilities had a written protocol for treating patients exposed to hazardous materials. Of the emergency care facilities, 12 (13%) had evacuated their emergency department or other parts of the hospital because of a hazardous materials exposure at least once during the previous five years. Overall, 71 (75%) emergency care facilities did not meet all of our criteria for hazardous materials incident preparation, including designated decontamination facilities; a plan for evacuating the facility when the source of contamination was from spills, contaminated patients, or both; and a written protocol for treating patients with exposure to hazardous materials.

Larger facilities (>72 inpatient beds, n = 48) were more likely than smaller facilities (≤72 inpatient beds, n = 47) to have designated decontamination facilities (OR, 2.3; 95% CI, 1.0 to 5.3). Larger facilities were also more likely to have protocols for handling chemical contamination and evacuation following hazardous materials spills (OR, 3.7; 95% CI, 1.4 to 9.6), for handling chemical contamination and evacuation following the treatment of contaminated patients (OR, 2.7; 95% CI, 1.2 to 6.2), and for treating patients exposed to hazardous materials (OR, 2.5; 95% CI, 1.1 to 5.6).

The occurrence of hazardous materials incidents in Washington State from 1992 to 1994 is reported in Table 3. The county population for the 39 counties in the state ranged from 2,305 to 1,587,505 (median, 45,865 inhabitants). Hazardous materials incidents occurred most frequently in counties with large populations; county population was highly correlated with the 1992 to 1994 counts of total number of hazardous materials incidents by county (R^2, 0.93), total number of victim incidents by county (R^2, 0.98), and total number of exposure victims by county (R^2, 0.92).

TABLE 3.—*Washington State Hazardous Materials Incidents By County (n = 39)**

Incidents	*Range*	*Median*
Total hazardous materials incidents	0–348	11
Incidents involving human exposure	0–91	2
Total exposure victims	0–371	7

*From Washington State Department of Health data, 1992–1994.[1]

Discussion

The results of this survey suggest that a significant percentage of Washington State emergency care facilities, by their own assessment, are not well prepared to provide care for patients with exposure to hazardous materials. Preparation should ideally include both the development of protocols for hazardous materials incidents and implementation through emergency preparedness drills, as required under JCAHO standards. Although the JCAHO standards concentrate on hazardous materials spills within hospitals, the two incidents described in this report demonstrate that secondary contamination occurring during the treatment of contaminated patients can also result in the need for evacuating emergency care facilities. For adequate preparedness, hospitals should have designated decontamination facilities, protocols for the treatment of contaminated patients, and protocols for handling chemical contamination and possible evacuation of their emergency department and other hospital areas when exposure to hazardous materials occurs.

Although we were not able to identify a previous survey of hospital preparedness for hazardous materials incidents, several authors have commented on disaster preparedness and the treatment of patients with chemical exposure.[8–12] A common theme of these articles is that hospital disaster preparedness was often inadequate. Given the strong correlation between county population and total number of hazardous materials incidents, victim incidents, and exposure victims by county, emergency care facilities in more populated counties should have a greater chance of encountering patients with chemical exposure. Although specific facilities such as trauma centers are often designated to receive hazardous materials exposure victims, contaminated patients may show up at any facility.

The limitations of this study include those typical of questionnaire survey studies. It was not easy to verify the accuracy of the information provided, although the respondents were generally key administrative personnel. Both underreporting and overreporting were possible. For example, institutions may have had protocols for handling hazardous materials exposures of which the respondents were unaware. Prudent medical practice and JCAHO standards, however, require not only the existence of emergency plans but also the implementation and periodic drilling of these protocols. If applicable emergency protocols were available, the lack of awareness of such protocols by key administrators would strongly suggest ineffective implementation. Studies using on-site inspection and surveys in other states would verify and further define the generalizability of our findings.

The equipment and training required for radioactive or chemical isolation and decontamination are not specified in the JCAHO standards. Although separate ventilation and water collection systems provide the greatest margin of safety and chemical control, the provision of these facilities may not be necessary or cost-effective for many institutions. In contrast to primary hazardous materials spills, the extent of chemical contamination present on the skin and clothing of exposed persons will often be within the water treatment capability of municipal water systems. As part of the planning process, hospitals should check with their local municipal systems to determine the need for separate water containment systems. Portable outside decontamination facilities are, by definition, separate from the hospital ventilation system. These may be the most cost-effective means of providing adequate patient care and satisfying existing standards, given the infrequent need of most emergency care facilities to do decontamination. Other options may include using the hospital morgue, which often has separate water containment and ventilation systems, as a designated decontamination facility.

Conclusion

Despite the frequent occurrence of hazardous materials incidents, most emergency care facilities in Washington State are not fully prepared to handle patients contaminated with hazardous chemicals. Although some general guidelines exist,[13,14] it would be useful for government and professional organizations to make available template protocols for the management of hazardous materials incidents to improve hospital preparedness. The provision of simple and relatively inexpensive portable outside decontamination units, with access to hot and cold running water, should also be encouraged. From a regulatory perspective, safety and health plans for hazardous materials incident sites should take into consideration the extent of hospital preparedness, with a designated and prepared emergency care facility available for the treatment of exposed persons.

Acknowledgment

Lucy Harter, of the Washington State Department of Health, Office of Toxic Substances, helped in obtaining data from the Hazardous Substances Emergency Event Surveillance System database.

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Articles

Health Care Professionals' Willingness to Do Mouth-to-Mouth Resuscitation

B. ZANE HOROWITZ, MD, *Portland, Oregon, and* LEONA MATHENY, RN, MN, *Sacramento, California*

To assess the willingness of physicians and nurses with training in basic cardiac life support to provide mouth-to-mouth resuscitation in both hospital and out-of-hospital settings, we surveyed all attendees at a monthly advanced life support course over a 1-year period. Of 622 attendees, 379 (61%) responded to our survey describing a variety of cardiac arrest scenarios. Less than half of the participants surveyed were willing to do mouth-to-mouth resuscitation on an unknown adult, male or female, who had collapsed in a supermarket. Overall, the group was willing to do mouth-to-mouth resuscitation on victims known to them: their neighbors (84%), children at a pool (88%), spouses (94%), and parents (93%). In the hospital setting, knowing a patient's human immunodeficiency virus (HIV) status greatly influenced the willingness to do mouth-to-mouth rescue. If a patient's HIV status was unknown, only a third of providers would do mouth-to-mouth resuscitation; if the HIV status was known to be negative, two thirds would do mouth-to-mouth resuscitation ($P < 0.002$), Children in the hospital whose HIV status was unknown would receive mouth-to-mouth resuscitation by 57% of the respondents. Children known to be HIV-negative would be resuscitated by 79% of the respondents. Co-workers were more willing to resuscitate a known physician or nurse than an unknown co-worker, with physicians more willing than nurses to do mouth-to-mouth resuscitation on an unknown co-worker. A third of the group has performed mouth-to-mouth resuscitation previously. Although an increased percentage of this subgroup was willing to provide mouth-to-mouth in all adult hospital scenarios, experienced providers of mouth-to-mouth wanted to receive mouth-to-mouth resuscitation less frequently (75%) than inexperienced providers (84%) ($P = 0.02$). The self-reported willingness to provide mouth-to-mouth resuscitation is influenced by patient characteristics; as the level of familiarity with the victim decreased, so did the willingness of the health care professional to do mouth-to-mouth.

(Horowitz BZ, Matheny L. Health care professionals' willingness to do mouth-to-mouth resuscitation. West J Med 1997; 167:392–397)

The first link in the chain of resuscitation is effective early cardiopulmonary resuscitation (CPR), which includes mouth-to-mouth resuscitation.[1,2] In an era wherein transmissible diseases such as the acquired immunodeficiency syndrome (AIDS) and hepatitis deter many lay people from performing mouth-to-mouth resuscitation, we wondered how health care professionals would respond to an unexpected need to start mouth-to-mouth resuscitation on someone. Although we encourage the use of a pocket mask for protection, as recommended by the Centers for Disease Control and Prevention,[1] we know that a health care professional may encounter a situation in which a response is required and no protective mask is available. Would physicians and nurses be more likely to do mouth-to-mouth resuscitation in a public place, such as a swimming pool or a supermarket, or when they were on duty in a hospital? Would knowing the victim's human immunodeficiency virus (HIV) status matter? Would a child evoke a better response than an adult?

To answer these questions, we selected a group of health care professionals with training in basic CPR and posed a series of scenarios to them. We compared the responses of physicians and nurses and those who had previously done mouth-to-mouth resuscitation with those who had not. The self-reported attitudes of health care professionals at an urban California teaching medical center are described in our report.

From the Division of Emergency Medicine and the Center for Continuing Nursing and Medical Education, University of California, Davis, Medical Center, Sacramento; and the Oregon Poison Center, Oregon Health Sciences University, Portland.

Reprint requests to B. Zane Horowitz, MD, Oregon Poison Center, Mail Code CB 550, Oregon Health Sciences University, 3181 SW Sam Jackson Park Rd, Portland, OR 97201-3098.

TABLE 1.— *Willingness of Physicians and Nurses to Provide Mouth-to-Mouth Resuscitation on Patients in a Hospital*

Patient Description	Survey Respondents			P Value
	Overall, %	MDs, %	RNs, %	
Man: HIV- and hepatitis-negative				
Medical floor	62	67	61	0.38
Surgical floor	64	67	63	0.57
Woman: HIV- and hepatitis-negative				
Medical floor	65	67	64	0.69
Surgical floor	64	67	63	0.62
Male: unknown				
Medical floor	36	36	37	0.81
Surgical floor	35	36	36	0.97
Female: unknown				
Medical floor	35	36	37	0.86
Surgical floor	35	36	36	0.97
Pediatric patient				
HIV- and hepatitis-negative	79	78	80	0.71
HIV or hepatitis unknown	57	55	60	0.39

HIV = human immunodeficiency virus.

Subjects and Methods

Advanced cardiac life support (ACLS) courses were given on a monthly basis by the University of California, Davis, Center for Continuing Nursing and Medical Education, an affiliate member of the Golden Empire Chapter of the American Heart Association. All students enrolled in the ACLS courses between May 1994 and June 1995 were given a survey form on registering. As a prerequisite for enrolling in the course, a current basic cardiac life support (BCLS) card was required; therefore, all persons answering the questionnaire were trained to do mouth-to-mouth resuscitation. Although answering the questionnaire was not required of any course participants, they were encouraged during all coffee breaks to complete and turn it in. Of a total of 622 course participants, 379 returned completed questionnaires, for a return rate of 61%. Descriptive statistics were performed using Excel (Microsoft). Pearson's χ^2 analysis was done using the Statistical Package for the Social Sciences.

Results

Of the 379 participants in ACLS courses who completed a questionnaire, 78 (20%) were physicians, 238 (63%) were nurses, and 63 (17%) were a diverse group that included paramedics, pharmacists, respiratory therapists, and other medical personnel. All participants held a degree in a field that provides health care.

Of the entire group, 47% and 49%, respectively, were willing to do mouth-to-mouth resuscitation on an unknown man and an unknown woman who collapsed in a supermarket. The physicians as a group were more willing to do mouth-to-mouth than the nurses, although this percentage did not reach statistical significance (56% versus 44%, $P = 0.075$). Overall, respondents were more willing to do mouth-to-mouth on victims known to them. They would perform mouth-to-mouth on a neighbor (84%), a child at a public swimming pool (88%), and a child in their own backyard pool (92%). There was no statistical difference between physicians and nurses in these scenarios.

In the case of a person who had collapsed on the street and was presumed to be homeless, only a few would perform mouth-to-mouth resuscitation on an adult (21% on a homeless man, 22% on a homeless woman). Most, however, would still do mouth-to-mouth on an apparently homeless child (55%). Of those who would not perform mouth-to-mouth resuscitation, all acknowledged that they would stop and call 911 for assistance.

In scenarios involving patients in a hospital, striking consistencies were found between physicians and nurses (Table 1). When presented with a male or a female patient on either medical or surgical floors who was known to the professional through their medical record to be negative for HIV and hepatitis, two thirds of all respondents would begin mouth-to-mouth resuscitation if no pocket mask were available. When the scenario was altered to a patient with unknown HIV or hepatitis status, only a third of health care professionals would initiate mouth-to-mouth resuscitation. Most respondents would wait until resuscitation equipment arrived. There was no statistical difference between physicians and nurses in these cases ($P = 0.81$ for male patient; $P = 0.86$ for female patient).

Given a scenario involving a child, most health care professionals would begin mouth-to-mouth resuscitation even without knowing the patient's HIV or hepatitis status. Overall, 57% would do mouth-to-mouth on an unknown child on a pediatric ward, with 79% willing to do so if they knew the child to be negative for HIV and

TABLE 2.—*Effect of Experience on the Willingness to do Mouth-to-Mouth Resuscitation: Prior CPR Providers and Never-CPR Providers*

Patient Description	Performed CPR			P Value
	Overall, %	Prior, %	Never, %	
Supermarket				
Man	47	52	44	0.139
Woman	49	56	46	0.058
Homeless person				
Man	21	25	19	0.178
Woman	22	25	20	0.291
Child	55	61	52	0.085
Man: HIV- and hepatitis-negative				
Medical floor	62	70	58	0.031*
Surgical floor	64	73	59	0.008*
Woman: HIV- and hepatitis-negative				
Medical floor	65	72	61	0.030*
Surgical floor	64	72	59	0.016*
Man: unknown				
Medical floor	36	42	33	0.087
Surgical floor	35	41	32	0.084
Woman: unknown				
Medical floor	35	41	33	0.117
Surgical floor	35	41	32	0.084
Pediatric patient				
HIV- and hepatitis-negative	79	84	76	0.107
HIV or hepatitis unknown	57	60	56	0.451

CPR = cardiopulmonary resuscitation, HIV = human immunodeficiency virus.

*Statistically significant.

hepatitis. Nurses were slightly more likely than physicians to perform mouth-to-mouth resuscitation on children, but the difference did not reach statistical significance (60% versus 55% for unknown child, $P = 0.39$; 80% versus 78% for known child, $P = 0.71$).

Although most health care professionals would respond to the aid of a co-worker who required mouth-to-mouth resuscitation, a known co-worker would more likely receive mouth-to-mouth resuscitation than an unknown co-worker. Whereas 74% and 72%, respectively, would do mouth-to-mouth resuscitation on a nurse or physician known to the health care professional, overall 60% and 57%, respectively, would do mouth-to-mouth on an unknown nurse or physician who collapsed at work. Physicians were statistically more willing than nurses to do mouth-to-mouth resuscitation both on a physician they never worked with before (79% versus 58%, $P = 0.009$) and on a nurse they never worked with before (76% versus 58%, $P = 0.006$).

When asked if they had ever performed mouth-to-mouth resuscitation, 34% of the ACLS class participants said they had. When this subgroup was analyzed as to their willingness to do mouth-to-mouth resuscitation compared with the group who had never performed it, the experienced group was more willing to do mouth-to-mouth in all the scenarios given. This reached statistical significance only in adult scenarios where the HIV status of the patient was known (Table 2). The only scenario in which the previous mouth-to-mouth provider answered affirmatively less often than the never-done mouth-to-mouth group is if they wanted mouth-to-mouth resuscitation done on themselves. Overall, 80% wished to have mouth-to-mouth resuscitation done if they collapsed, but whereas 84% of participants who had never done mouth-to-mouth desired it for themselves, only 75% of those who had previously done it wanted someone else to do it to them if the need arose ($P = 0.021$).

In scenarios in which a parent or spouse collapsed and required CPR, nearly all responders in all subgroups said they would begin mouth-to-mouth resuscitation (93% to 96%). When asked if their spouse or housemate knew CPR, 71% responded that they did, with nurses living with a trained CPR provider (76%) more often than physicians (63%) ($P = 0.010$).

Discussion

The decision to do mouth-to-mouth resuscitation is a personal one influenced by a variety of factors. In our study, most health care professionals would hesitate to perform mouth-to-mouth resuscitation on a homeless adult, an unknown patient, and to a lesser degree, on an adult who collapsed in a supermarket. But perhaps

because of the younger age and the reflexive response a sick child evokes from health care professionals, most would not hesitate to perform mouth-to-mouth on a child in or out of a hospital, even if the child's HIV status was unknown.

Respondents to our survey were asked to provide optional written comments. Most comments noted a fear of acquiring AIDS, HIV infection, hepatitis, tuberculosis, and herpes in their decision not to do mouth-to-mouth resuscitation in some cases. A few qualified their response that they would normally do mouth-to-mouth unless they saw blood, vomit, or open lesions in the airway. Some physicians or nurses felt that CPR training carried with it a responsibility to do mouth-to-mouth resuscitation or felt a moral responsibility to always do it. Still others commented that they always carried a pocket mask so that they could respond appropriately and administer mouth-to-mouth resuscitation.

Among respondents unwilling to do mouth-to-mouth, they wrote that they thought that the code team response was fast enough that they would rather wait until the proper equipment arrived before beginning CPR. Those who would withhold mouth-to-mouth ventilation also expressed concerns regarding a greater responsibility to their own family to not get sick or pondered whether the hospital would take care of them for life if they acquired HIV.

Although we left the scenario of a homeless adult purposefully vague, they were the least likely persons in our survey to receive mouth-to-mouth rescue if they needed it. No physical description or health history was provided for these scenarios, so the unwillingness of health care professionals to do mouth-to-mouth resuscitation on this group reflects their personal biases about the homeless. Although most respondents gave no specific comments to this scenario, a few said they would not do mouth-to-mouth on the homeless because they were likely to have collapsed as a result of drug or alcohol abuse and therefore were in a higher risk group for HIV.

Lay Personnel

A previous study regarding mouth-to-mouth resuscitation highlights the fear of acquiring an infectious disease in both lay people and health care workers. In a post-course survey of predominantly lay people taking a four-hour CPR course in southern California,[3] it was found that although 92% would do CPR on a stranger, that percentage dropped to 32% if the rescuer was told that the collapsed victim had AIDS. Despite those results, other surveys suggest a substantial hesitancy to do mouth-to-mouth on an unknown victim. In a survey of both lay people and health care professionals in Arizona,[4] few of whom had CPR training, only 16% said they would do CPR on a stranger, but 74% would do it on a friend or relative who collapsed. This is consistent with our results in which 72% to 74% would do mouth-to-mouth on a known collapsed co-worker and 94% would do CPR on a spouse or parent.

Basic Life Support Providers

In a previous study, training in CPR did not notably increase the willingness of health care professionals to do mouth-to-mouth resuscitation. Instructors in basic life support were less likely to perform mouth-to-mouth resuscitation in scenarios in which HIV exposure was a possibility.[5] In a survey of 1,794 BCLS instructors, only 10% would do CPR on a person with heroin overdose, 18% on a man on a bus in San Francisco, and 29% on a man at a football game in New York City. But 97% would do it on a drowning child, and 54% would do it on a female college student. Of these BCLS instructors, 49% had actually done mouth-to-mouth resuscitation previously, and 40% of this subgroup would hesitate to do it again. They also stated that they had observed other BCLS providers hesitate to do CPR 40% of the time. In our study, previous providers of mouth-to-mouth resuscitation reported an increased willingness to do mouth-to-mouth.

Health Care Professionals

In a series of studies from southern California, a great unwillingness of health care professionals to do mouth-to-mouth resuscitation was suggested.[6–8] In a survey of internists and nurses in which cardiac collapses outside the hospital were described, only 5% of licensed vocational nurses, 10% of registered nurses, 16% of attending physicians, and 21% of resident physicians were willing to do mouth-to-mouth on a "well-dressed male in his mid-20s in a trendy bookstore in a gay neighborhood." The same group were more likely to do CPR on a man in a grocery store whom they never saw before (20% to 21% for nurses, 54% to 57% for physicians), and on a child who collapses (resident physicians 99%, attending physicians 81%, registered nurses 75%, and licensed vocational nurses 82%). With the exception of the low percentage of nurses in these studies who were willing to do mouth-to-mouth in the grocery store, our percentages for other scenarios appear similar, showing the same trend to hesitate with victims in less-known situations. Interestingly, an associated study showed that 92% of homosexual men surveyed at a gay restaurant or participating in an AIDS walk-a-thon were willing to provide mouth-to-mouth resuscitation on an unknown man.[7] The homosexual group would also do mouth-to-mouth on 95% of children. If the homosexual group were asked to provide mouth-to-mouth resuscitation if they themselves were HIV-positive, most would still provide it in 87% of all scenarios. It was speculated that the homosexual community, through aggressive education efforts, correctly believes that HIV is not transmissible through saliva.

It has been shown, however, that the same level of awareness about AIDS in physicians still makes them unlikely to do mouth-to-mouth resuscitation.[8] In a study in 1994 in which 74 house staff were surveyed at a Los Angeles teaching hospital, 33 (45%) were willing to do mouth-to-mouth on a 45-year-old heart attack victim, 29

(39%) were willing to do mouth-to-mouth on an elderly nursing home patient, 12 (16%) were willing to do mouth-to-mouth on a trauma patient with blood around his mouth, and only 5 (7%) were willing to do it on a 32-year-old man admitted to the hospital with fever, weight loss, and pneumonia. In this group, all respondents had both BCLS and ACLS training and might as a part of their duties be required to respond to an in-hospital CPR code. Although our questionnaire was less specific as to case descriptions, we found only a third of our physicians willing to provide mouth-to-mouth resuscitation to an unknown patient on a medical or surgical floor, but two thirds willing if they knew the patient to be HIV-negative. Physicians were more willing than nurses to come to the aid of an unknown co-worker who collapsed in the hospital. This was the only scenario in our study comparing physicians' and nurses' willingness to do mouth-to-mouth resuscitation that showed a statistical difference between physicians and nurse.

Physicians' Wish to Receive Mouth-to-Mouth Resuscitation

One of every five respondents in our survey did not wish to receive mouth-to-mouth resuscitation if they had a cardiac collapse. Of those who had done CPR before, 25% expressed a desire to not have it done on them. This correlates with results from other similar surveys. In a set of surveys of health care professionals at Stanford University Medical Center (Palo Alto, California), the request for a personal "no-code" was found to vary by level of training.[9,10] A no-code status was requested by 36% of medical students, 25% of nurses, 19% of resident physicians, and 13% of attending physicians. When this group was asked to suppose they had AIDS, the medical students wanted a no-code status 71% of the time, resident physicians 90% of the time, and attending physicians 87% of the time.

Similar results were found among 72 resident physicians surveyed in Portland, Oregon.[11] Although all respondents in the group wanted to be resuscitated if they had an acute myocardial infarction at age 40, only 28% would at age 80. No one in the group would want to be resuscitated if they were 80 years old and had any of the following: Alzheimer's disease, congestive heart failure, emphysema, or cirrhosis. Thirty percent would want to be resuscitated if they had AIDS at age 40, and 5% would want to be resuscitated with AIDS at age 80.

Are There Alternatives to Mouth-to-Mouth Resuscitation?

Mouth-to-mouth resuscitation is taught to more than 4 million people every year.[7] If all providers were to follow the recommendations from the Centers for Disease Control and Prevention and the American Heart Association and purchase a $3 personal pocket mask, it would cost $12 million. Many of our respondents claimed to have done just this in case they were needed to do mouth-to-mouth resuscitation outside the hospital. New York City has enacted a law placing such devices in public areas.[6] This might solve the problem of people's hesitating to do mouth-to-mouth resuscitation. In one study, a commercially available mask was used in a test broth containing the HIV virus. After the broth was ventilated through this mask, cultures for HIV remained negative after a month.[12] In a test of the ability to culture oral bacteria from pocket masks immersed in a broth of bacteria, all commercially available masks were found to be impermeable.[13] Six of eight commercially available barrier devices, however, failed to prevent the spread of oral flora to the rescuer side of the device.[13]

A few respondents in our survey insisted that in the hospital, resuscitation equipment should be immediately available. The cost of placing bag-valve-mask resuscitation equipment at each bedside would be exorbitant. Most patients who have a cardiac arrest in hospital end up waiting for the crash cart or code team to respond. But resuscitation rates from in-hospital arrest still have a 10% to 25% discharge rate[8] (our facility has a 16% survival-to-discharge rate), compared with out-of-hospital resuscitation rates of less than 10%. Further study is required to see if the immediate availability of bag-valve-mask devices increased the survival-to-discharge rate and if it justified the cost.

The time to respond with any type of resuscitation may be more important than the initiation of mouth-to-mouth. In Milwaukee, bystander CPR was not shown to improve discharged-alive rates,[14,15] whereas in Arizona it was thought to have an effect, with no successful resuscitations occurring unless bystander CPR was performed.[16] The results of one study of animals suggest that chest compressions without ventilations are as efficacious as standard CPR.[17] In Belgium, incorrect bystander CPR without ventilations produced a survival rate of 10%, whereas correct CPR with ventilations had a survival rate of 16%.[18]

We are encouraged that our results suggest a willingness by health care professionals to do mouth-to-mouth resuscitation. Bystander CPR will probably continue to be done for children, relatives, friends, and a few strangers. Although we encourage our health care professionals to use a pocket mask, the time may come that a health care professional must make a decision to provide mouth-to-mouth without one. Although the risk of AIDS transmission from CPR remains remote, it can never be said to be nonexistent if open wounds or blood contaminates the procedure. Whereas preliminary data suggest that even CPR without mouth-to-mouth ventilation is better than no CPR at all, we cannot advocate not providing mouth-to-mouth resuscitation when the need arises.

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Articles

Pulmonary and Allergy Subspecialty Care in Adults With Asthma

Treatment, Use of Services, and Health Outcomes

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To study the relationship between physician subspecialty practice type and health measures in patients with adult asthma, we prospectively studied 601 adults with asthma. The subjects were recruited from a random sample of board-certified pulmonary or allergy internal medicine subspecialists practicing in northern California; 539 patients (90%) were restudied after 18 months. Structured telephone interviews were used to elicit demographics, clinical variables, and measures of asthma severity, asthma-specific quality of life, and physical function status. At baseline and follow-up, 283 subjects (53%) reported their principal asthma care provider type as a pulmonary specialist throughout and 150 (28%) as an allergy specialist throughout, 53 (10%) switched provider type during follow-up, and 53 (10%) reported that their principal asthma care physician was from neither subspecialist group. Taking into account illness severity and other demographic and clinical covariates, the group whose principal asthma care came from an allergy subspecialist was more likely than the pulmonary specialist-care group to report possessing a peak expiratory flow rate meter (odds ratio [OR], 2.8; 95% confidence interval [CI], 1.8 to 4.6) and less likely to be receiving high-dose inhaled steroids (OR, 0.3; 95% CI, 0.1 to 0.6). Taking into account demographic and clinical covariates, allergists' care was related to worse subject-reported asthma-specific quality of life ($P = 0.02$), but not to statistically increased risk of hospitalization, decreased physical function, or an increased number of reported health-related restricted-activity days. We observed subject-reported specialist variation in management and health outcomes among adults with asthma not accounted for by differing disease severity or other clinical and demographic variables.

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Asthma among adults is common and costly and appears to be rising in incidence and prevalence.[1–6] Of all ambulatory care visits in the United States, 1% have been estimated to involve asthma as the primary medical diagnosis, whereas among internal medicine specialists, asthma accounts for an even higher proportion of such visits, making it the 13th most common diagnosis in ambulatory care visits for that group.[1,7]

Although characteristics of physicians and their practice style have been recognized as important possible factors affecting health outcomes generally,[8,9] information on practice variation in asthma and its possible effect is scant. A recent national survey found wide-ranging differences in asthma management by practice specialty.[10] For example, although 76% of allergy subspecialists instructed their patients on monitoring peak expiratory flow rates (PEFR), this proportion fell to 56% among pulmonary subspecialists, even though this is a key component of current National Heart, Lung and Blood Institute guidelines aimed at better asthma control.[11,12] A limited number of other studies have examined differences in outcomes following allergy subspecialist care of asthma compared with that of generalists.[13–18] Despite practice differences between pulmonary and allergy specialists noted previously,[10] however, none of the outcome studies have included pulmonary specialists.

We examined a variety of practice and outcome measures for adults with asthma who were cared for by pul-

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ABBREVIATIONS USED IN TEXT

CES-D = Centers for Epidemiological Studies Depression [scale]

CI = confidence interval

HMO = health maintenance organization

OR = odds ratio

PEFR = peak expiratory flow rate

SF-36 = Medical Outcomes Study Short-Form General Health Survey

monary or allergy subspecialists. We hypothesized that, even after taking illness severity and other covariates into account, both clinical practice and health outcomes would differ by subspecialist-treatment group. We addressed this question by analyzing data from an ongoing panel study of adults with asthma initially identified through a random sample of medical specialists.[19]

Subjects and Methods

Overview

The persons with asthma we studied are part of an ongoing panel derived from a random sample of northern California internists board-certified in the subspecialties pulmonary or allergy immunology. Participating physicians maintained a registry of all patients seen with asthma in the outpatient setting over one to two months, depending on their patient volume. A trained survey worker administered a structured, closed-ended, computer-assisted, telephone interview lasting 45 minutes to each person with asthma who agreed to participate in the study when contacted first by mail and then by telephone. At baseline, we also obtained spirometry data, if available, from the recruiting physicians. We carried out follow-up interviews 18 months after the baseline survey. The follow-up interview was similar to the baseline survey and was administered by the same person.

Subject Recruitment for Baseline Interview

The details of the initial subject recruitment have been reported previously.[19] In brief, we obtained a list for northern California of all internal medicine specialists who were also board-certified pulmonary (n = 252) or allergy immunology subspecialists (n = 40). Of 145 randomly selected pulmonary subspecialists, 92 were eligible (had at least one full day of outpatient practice per week in northern California). Of these, 68 agreed to participate. Of 20 allergists selected, 19 were eligible and 17 participated. Overall, 8 recorded no patients, and 3 others listed a few names of which none entered the study. The final number of participating subspecialists from whom subjects were successfully enrolled and studied was 74, of whom 57 were pulmonary and 17 allergy subspecialists.

Patient enrollment criteria were as follows: age 18 through 50 years, asthma clinically consistent with American Thoracic Society and American College of Chest Physicians definitions, and no concomitant chronic bronchitis or emphysema. Other factors such as age of asthma onset, severity, atopy, or smoking history were not eligibility or exclusion criteria.

We attempted to recruit each potential subject registered. Of 698 eligible subjects registered, 84 (12%) declined to participate and 13 (2%) were not successfully contacted, for an overall study participation of 601 (86%) at the time of the baseline interview. Of these, 384 (64%) were recruited from pulmonary and 217 (36%) from allergy subspecialty practices. Study participation rates did not differ significantly by specialty recruitment type (87% versus 84%, $P > 0.5$). The number of participants recruited per practice site, however, was greater from allergy (median, 9) than from pulmonary (median, 5) specialists ($P < 0.05$).

Subject Follow-up

We reinterviewed 539 (90%) of 601 adults with asthma previously studied at baseline. The mean number of months elapsed to reinterview was 18.6 ± 1.0 standard deviation (median, 18.4 months). Of the 62 subjects not reinterviewed, 5 had died in the interim (3 deaths were attributed to asthma). Of the remaining subjects not restudied, 47 returned survey postcards offering the option to decline an interview, as required by the University of California, San Francisco, Committee on Human Research, and 10 subjects were lost to follow-up.

Of those reinterviewed, 343 (64%) were originally recruited from pulmonary practices; 41 (66%) of those not reinterviewed were recruited from pulmonary practices ($P > 0.8$). Those not studied at follow-up were younger (36.0 ± 9.2 versus 39.4 ± 8.1 years; $P = 0.003$) and were more frequently male (28 [45%] versus 160 [30%]; $P = 0.02$), but the ethnic-racial mix did not differ statistically (white, non-Hispanic, 26 [58%] versus 364 [68%]; $P = 0.18$). There was no statistical difference in disease severity between subjects who were retained (severity score, 11.3 ± 5.9) and those not reinterviewed (score, 10.5 ± 6.9; $P > 0.2$).

Definition of Principal Asthma Care Physician

A total of 283 subjects (53%) identified their principal asthma care physician as a pulmonary subspecialist both at baseline and at the follow-up interview. Of these, 17 (6%) reported physician visits with an allergy subspecialist at least once during the preceding 18 months. Of 539 subjects, 150 (28%) identified an allergy subspecialist as their principal asthma care physician at both interviews. Of these, 6 (4%) reported at least one physician visit with a pulmonary subspecialist in the preceding 18 months. Over the course of follow-up, 53 (10%) changed the subspecialist they identified as their principal asthma care physician, either from pulmonary to allergy (n = 42) or from allergy to pulmonary (n = 11).

Finally, 53 other subjects did not identify either a pulmonary or allergy subspecialist as their principal asthma care physician at the time of both baseline and follow-up interviews. Because of subject recruitment, all subjects

in this group had been evaluated or treated by a physician from one of these two subspecialist groups before the baseline interview: 38 (72%) were initially recruited from pulmonary and 15 (28%) from allergy subspecialty practices. None, however, reported being cared for by a subspecialist as their principal asthma care physician throughout the 18-month follow-up. At follow-up, 18 (34%) of these 53 subjects reported no regular asthma care health professional of any kind since baseline; 18 (34%) reported some follow-up since baseline with either a pulmonary or allergy subspecialist; and 17 (33%) reported other, nonsubspecialist asthma medical follow-up only.

Interviews and Survey Instruments

The baseline and follow-up interviews included questions covering asthma history, symptoms, and treatment; general health and functional status; and demographic and psychosocial variables. We quantified asthma severity using a validated scoring system derived from the questionnaire responses.[19,20] The severity-of-asthma score is a composite of the following variables: frequency of current asthma symptoms, past asthma hospital admissions and mechanical ventilatory support for asthma, past and current use of oral and parenteral corticosteroids, and the use of asthma medications other than oral and parenteral steroids. A maximum score of 28 reflects the greatest asthma severity.

The survey also included a validated, asthma-specific quality-of-life instrument (Marks and Woolcock) based on a 20-item Likert-type scale. This instrument analyzes four areas: breathlessness, mood, social functioning, and health concerns.[21] A maximum summary score of 80 reflects the greatest adverse effects of asthma on the quality of life.

We also included in the interview the 36-question battery (SF-36) derived from the Medical Outcomes Study Short-Form General Health Survey.[22,23] The SF-36 includes subscales in several domains, of which the subscales for self-perceived general health status (based on responses to 6 questionnaire items) and physical function (based on responses to 10 questionnaire items) were of particular interest. A maximum of 100 points reflects better general health or physical function. Although the SF-36 includes a mental health subscale based on 5 questions, we also included in our follow-up interviews the 20-item Center for Epidemiological Studies Depression (CES-D) scale as an alternative measure of this domain.[24] A maximum score of 60 on this scale reflects the greatest degree of depressive symptoms.

We defined other variables on the basis of structured interview responses. The atopic history was based on reported incidents of allergic rhinitis or atopic dermatitis. Family income was ascertained as a series of increments: <$5,000, $5,001 to $10,000, $10,000 increments through $50,000, 50,001 to $75,000, and >$75,000. To convert to specific income levels, the midincrement value was applied, except for the highest category, where a value of $87,500 was applied. For insurance status, respondents were first asked if they had any health insurance and then to specify the type and provider. We specifically asked if coverage was provided by the Kaiser Permanente Health Plan, the largest staff-model health maintenance organization (HMO) in the region, by one of a series of other prominent HMOs in the region, or by several large third-party insurers. The interviewer prompted each by name.

Data Management and Statistical Analysis

Computer-assisted interview software was used. Interview data were exported into a PC-SAS (SAS Institute, Cary, NC) compatible format. We tested the differences between those reinterviewed and those not studied at follow-up by either the χ^2 or t test. We tested the differences between four groups defined by principal asthma provider type using either the χ^2 (categorical variables) or analysis of variance (continuous variables) or, for nonparametric analyses of continuous variables, the Kruskal-Wallis equivalent of the Wilcoxon rank-sum test. Pairwise comparisons of severity-of-asthma score used Tukey's modified t test.

To control for differences in asthma severity and other covariates, we reexamined these differences using multiple-regression analyses. We used multiple-logistic-regression analysis to estimate associations between principal asthma care physician type and those medical treatments (pneumococcal vaccination, PEFR meter provision, allergy desensitization immunotherapy, and high-dose inhaled steroids) that differed significantly by physician type in an initial bivariate analysis.

We also used multiple-logistic-regression analysis to estimate the association between subspecialty care and acute care services use for asthma: ≥2 urgent physician office visits; ≥2 emergency department visits; and ≥1 hospital admission over follow-up. Finally, we used multiple linear regression to estimate the association between principal asthma care physician type and the following outcome measures: asthma-specific quality-of-life score (the overall quality-of-life score and each of its 4 component domains), SF-36 physical function score, health-related activity-restricted days over the past 30 days, and the depression score measured by the CES-D battery.

In each model, we included the following possible confounding variables: age, sex, years of education, baseline income, change in income over follow-up, cigarette smoking status (>100 lifetime cigarettes), history of atopy, childhood asthma onset, severity-of-asthma score, general health status (SF-36), and health insurance status (HMO coverage at baseline and follow-up; non-HMO health insurance at baseline and follow-up; change between HMO and non-HMO during follow-up; uninsured for health care at baseline, at follow-up, or at both interviews). Finally, we reanalyzed the quality-of-life model, adding to it the four practice measures differing by principal asthma care physician: pneumonia vaccination, PEFR meter provision, high-

TABLE 1.—*Baseline Demographics by Principal Asthma Care Subspecialty Group*

	Principal Asthma Care Provider Type				
Demographic Variable	*Pulmonary (n = 283)*	*Allergy (n = 150)*	*Both (n = 53)*	*Neither (n = 53)*	*P Value**
White, non-Hispanic, no. (%)	194 (69)	97 (65)	37 (70)	36 (68)	>0.8
Female sex, no. (%)	199 (70)	97 (65)	39 (74)	44 (83)	0.08
Age, yr, mean ± SD	40 ± 8	40 ± 8	38 ± 8	37 ± 10	0.07
Education, yr, mean ± SD (median)	14 ± 3 (14)	15 ± 2 (14)	14 ± 2 (14)	14 ± 3 (13)	0.04
Married/partnered, no. (%)	186 (53)	99 (66)	37 (70)	29 (55)	>0.30
Persons in household					>0.50
1, no. (%)	28 (10)	14 (9)	6 (11)	6 (11)	
2, no. (%)	87 (31)	59 (39)	16 (30)	19 (36)	
3, no. (%)	70 (25)	34 (23)	8 (15)	9 (17)	
≥4, no. (%)	98 (35)	43 (29)	23 (43)	19 (36)	

SD = standard deviation.

*Differences were tested by χ^2 or Kruskal-Wallis (education).

dose inhaled-steroid use, and immunotherapy injections. We also tested the effect of recruitment group size.

Results

Demographics and Clinical Variables

Table 1 compares subject demographics by type of principal asthma care provider: pulmonary, allergy, both (subjects who switched between a pulmonary and allergy subspecialist over follow-up), and neither (neither subspecialist type was the principal asthma care physician throughout follow-up). Years of education varied statistically by asthma care physician type (Kruskal-Wallis, $P < 0.05$) and was highest in the allergist-treated group. Differences in sex and age were of borderline statistical significance ($0.05 \leq P < 0.10$); other demographic characteristics did not differ statistically.

Table 2 compares clinical variables by the principal asthma care physician. Asthma severity, measured on a 28-point scale, varied significantly by subspecialist type ($P = 0.01$). Severity was greatest among the pulmonary specialist-treated group; the mean pairwise difference in scores between the pulmonary and allergy subspecialist groups was 1.6 points ($P < 0.05$, Tukey's modified t test). Significantly more subjects with an atopic history were in the allergy specialist-treated group. The proportion of subjects who had ever smoked cigarettes regularly (>100 lifetime) also varied significantly, with the greatest proportion (43%) being cared for by pulmonary specialists. Current smokers (not shown in Table 2) numbered only 37 (7%) of the entire group and did not differ statistically by physician type ($P > 0.3$).

Table 3 shows that income and health insurance status varied significantly by principal asthma care physician. Income was highest at baseline in the allergy care

TABLE 2.—*Baseline Clinical Variables by Principal Asthma Care Provider Type**

	Principal Asthma Care Provider Type				
Clinical Variable	*Pulmonary (n = 283)*	*Allergy (n = 150)*	*Both (n = 53)*	*Neither (n = 53)*	*P Value*
Childhood asthma, no. (%)	120 (42)	79 (53)	23 (43)	22 (42)	0.20
Ever smoked, no. (%)	123 (43)	48 (32)	16 (30)	17 (32)	0.045
Atopic history, no. (%)	206 (73)	129 (86)	42 (79)	43 (81)	0.02
Severity score, mean ± SD†	12.1 ± 6.2	10.5 ± 5.0	10.0 ± 5.9	10.9 ± 6.2	0.01
General health, mean ± SD‡	53.5 ± 26	56.5 ± 24	62.2 ± 26	54.2 ± 24	0.11
FEV_1, % predicted, mean ± SD§	79 ± 23% (n = 179)	81 ± 21% (n = 110)	83 ± 25% (n = 39)	85 ± 21% (n = 34)	>0.30

SD = standard deviation

*Differences were tested by χ^2 or analysis of variance. All interview variables were taken at baseline.

†The severity score is based on past asthma history, medication use, and symptoms; a higher score reflects greater illness severity (maximum, 28).

‡General health refers to the general health status domain of the Medical Outcomes Study Short-Form 36-item survey instrument; a higher score (maximum, 100) reflects better respondent-perceived health status.

§The percentage of forced expiratory volume in 1 second (FEV_1%) was available for 362 subjects only.

TABLE 3.—*Income and Insurance Status at Baseline and at 18-Month Follow-up*

	Principal Asthma Care Pravider Type				
*Incame and Insurance**	*Pulmanary (n = 283)*	*Allergy (n = 150)*	*Bath (n = 53)*	*Neither (n = 53)*	*P Value†*
Annual income, thousands of dollars‡					
Baseline, median	25.0	31.3	22.5	22.5	0.01
At follow-up, median	25.0	31.3	31.3	17.5	<0.001
Income change, mean ± SD	0.7 ± 14	3.7 ± 13	3.4 ± 13	−2.3 ± 12	0.03
Health insurance status, no. (%)					
Baseline					<0.001
None	11 (4)	4 (3)	0 (0)	6 (11)	
HMO	166 (59)	112 (75)	29 (55)	22 (42)	
Other insurance	106 (37)	34 (23)	24 (45)	25 (47)	
At follow-up, no. (%)					<0.001
None	19 (7)	3 (2)	3 (6)	16 (30)	
HMO	157 (55)	106 (71)	27 (51)	19 (36)	
Other insurance	107 (38)	41 (27)	23 (43)	18 (34)	
Insurance changes, no. (%)					<0.001
Not covered	24 (8)	5 (3)	3 (6)	19(36)	
HMO throughout	126 (45)	100 (67)	24 (45)	11 (21)	
Other throughout	69 (24)	28 (19)	20 (37)	12 (22)	
Mixed coverage	64 (23)	17 (11)	6(11)	11 (21)	

HMO = health maintenance organizatian.

*Of those not covered by health insurance either at baseline or at follow-up (n = 51), 11 were without coverage at both interviews, 30 lost their coverage, and 10 gained coverage over follow-up.
†Differences tested by χ^2 or Kruskal-Wallis test.
‡Income refers to per-adult household income.

group and increased to the greatest degree over follow-up. Income fell among those not being seen by a subspecialist; this group also had the greatest proportion (36%) without health insurance coverage at baseline, follow-up, or the time of both interviews.

Clinical Practice and Treatment

Four asthma-related clinical practices differed significantly by principal asthma care physician group (Table 4). The proportion reporting pneumococcal vaccination

TABLE 4.—*Asthma-Related Treatments by Principal Asthma Care Subspecialty Group*

	Principal Asthma Care Physician Type				
Asthma Measures at Fallaw-up	*Pulmanary (n = 283), Na. (%)*	*Allergy (n = 150), Na. (%)*	*Bath (n = 53), Na. (%)*	*Neither (n = 53), Na. (%)*	*P Value**
Control strategies adopted					
Vaccinations					
Influenza, previous year	162 (57)	84 (56)	31 (58)	34 (64)	>0.7
Pneumococcal, ever	86 (30)	26 (17)	10 (19)	11 (21)	0.01
PEFR meter available	143 (51)	104 (69)	38 (53)	32 (60)	0.002
Ongoing immunotherapy	10 (4)	38 (25)	12 (23)	1 (2)	<0.001
Medication regimens†					
Inhaled steroid	176 (62)	103 (69)	35 (66)	29 (55)	>0.2
High-dose inhaled steroid	27 (10)	3 (2)	4 (8)	0 (0)	0.004
Regular inhaled β-agonist	186 (66)	101 (67)	33 (62)	34 (64)	>0.9
Without inhaled steroid	50 (18)	25 (17)	9 (17)	11 (21)	>0.9
Oral β-agonist/theophylline	127 (38)	64 (43)	17 (32)	20 (38)	>0.3
Without inhaled steroid	39 (14)	17 (11)	2 (4)	7 (13)	>0.2
Frequent oral steroids	53 (19)	23 (15)	9 (17)	7 (13)	>0.6

*Differences tested by χ^2 test.
†Inhaled steroids and β-agonist and oral β-agonist/theophylline refer to reported use for 2 wk before the follow-up interview. Regular inhaled β-agonist use is defined as ≥2 puffs/day on average. High-dose inhaled steroid is defined as ≥20 puffs/day. Frequent parenteral steroids is defined as used at least every other day for ≥3 months over the 18 mo before the interview.

TABLE 5.—*Subspecialty Follow-up and Treatment Strategies: Multiple-Logistic-Regression Analysis**

	Treatment Strategies Patentially Related ta Adult Asthma			
Predictar Variable	*Pneumacaccal Vaccinatian, OR (95% CI)*	*PEFR Meter, OR (95% CI)†*	*Immunatherapy, OR (95% CI)‡*	*≥20 Puffs Steraid, OR (95% CI)*
Principal asthma provider				
Pulmonary (referent)	1.0	1.0	1.0	1.0
Allergy	0.5 (0.3–0.9)	2.8 (1.8–4.6)	9.0 (4.1–19.6)	0.3 (0.1–0.6)
Both	0.6 (0.3–1.4)	1.6 (0.8–3.1)	8.5 (3.3–22.2)	0.4 (0.1–1.3)
Neither	0.9 (0.4–1.9)	2.1 (1.1–4.3)	0.7 (0.1–5.6)	1.0 (0.3–3.6)
Health insurance status				
Not covered (referent)	1.0	1.0	1.0	1.0
HMO over follow-up	2.6 (1.05–6.5)	1.6 (0.7–3.4)	3.2 (0.4–28.4)	4.1 (1.03–16.0)
Other over follow-up	2.4 (0.9–6.1)	0.8 (0.4–1.7)	4.1 (0.4–36.9)	1.2 (0.3–5.1)
Mixed HMO and other coverage	1.0 (0.4–2.6)	0.8 (0.4–1.8)	4.6 (0.5–43.1)	1.1 (0.3–5.1)
Baseline asthma severity	3.0 (2.0–4.6)	4.4 (2.9–6.6)	1.3 (0.7–2.4)	5.8 (3.0–11.4)

CI = confidence interval, HMO = health maintenance organization, OR = adds ratia

*The odds ratio for severity score and age is expressed per 10-unit change. The logistic regression model also includes baseline age, sex, SF-36 general health status (see text and Table 2 for description), education, atopic history, childhood asthma onset, history of ever smoking cigarettes, baseline per-adult family income, and change in income at follow-up from baseline.

†This treatment strategy involves the use of a PEFR meter.

‡The patient receives ongoing allergy desensitization.

was greatest (30%) among the pulmonary specialist-treated group and lowest (17%) among the allergy specialist-treated group. In contrast, the greatest proportion with PEFR meters (69%) was among the allergist-treated group and the lowest (51%) among those being treated by pulmonary specialists. The two other practices that varied statistically by provider subspecialty type were ongoing immunotherapy (allergy desensitization shots), which was most frequent among the allergist-treated group, and the use of high-dose inhaled steroids (≥20 puffs per day), which was most frequent among the pulmonary specialist–treated group. Other patterns of medication use did not differ statistically by physician type.

Table 5 presents a further analysis of these four treatment strategies in relation to principal asthma care physician, taking into account the possible confounding effects of health insurance status, asthma severity, and several other additional covariates. In this multiple-logistic-regression analysis, subjects in the allergist-treated group were statistically more likely than those in the pulmonary specialist–treated group to have a PEFR meter or to be receiving ongoing immunotherapy and were less likely to have ever received a pneumococcal vaccination or to be using high-dose inhaled steroids.

In the same models (Table 5), greater asthma severity assessed at baseline was a potent predictor of PEFR meter possession, pneumococcal vaccination, and the use of high-dose inhaled steroids at follow-up but was not a predictor of ongoing immunotherapy. Insurance coverage through an HMO reported at baseline and at follow-up was strongly associated with high-dose inhaled-steroid use and pneumococcal vaccination.

Health Care Use

As shown in Table 6, we observed only modest variation by principal asthma care physician type in each of three measures of acute asthma care use that we studied: urgent office visits, emergency department visits, and hospital admissions (although the last was of borderline statistical significance). Moreover, when we took into account multiple covariates of interest by multiple-logistic-regression analysis (Table 7), we found that the principal asthma care physician type was not a significant predictor of any of the usage variables we studied ($P > 0.05$).

TABLE 6.—*Asthma-Related Health Care Use by Principal Asthma Care Physician Type*

	Principal Asthma Care Physician Type				
Asthma Measures	*Pulmanary (n = 283), Na. (%)*	*Allergy (n = 150), Na. (%)*	*Bath (n = 53), Na. (%)*	*Neither (n = 53), Na. (%)*	*P Value**
Services used past 18 mo					
≥2 emergency department asthma visits	39 (14)	14 (9)	7 (13)	4 (8)	>0.3
≥2 Urgent MD office visits	47 (17)	29 (19)	12 (23)	5 (9)	>0.2
≥1 Hospital admission for asthma	36 (13)	8 (5)	6 (11)	3 (6)	0.06

*Differences tested by χ^2 test.

TABLE 7.—*Predictors of Asthma-Related Health Care Use: Multiple-Logistic-Regression Analysis**

Associated Factors	Measures of Acute Health Care Use for Asthma, Reported Frequency Over 18 Mo†		
	≥2 Urgent MD Office Visits, OR (95% CI)	≥2 Emergency Department Visits, OR (95% CI)	≥1 Hospital Admission, OR (95% CI)
Subspecialist follow-up			
Pulmonary (referent)	1.0	1.0	1.0
Allergy	1.6 (0.9–2.9)	1.0 (0.5–2.0)	0.7 (0.4–1.6)
Both	2.1 (0.96–4.7)	1.4 (0.5–3.7)	1.4 (0.5–4.2)
Neither	0.6 (0.2–1.8)	0.6 (0.2–2.0)	0.5 (0.1–2.0)
Health insurance status			
Not covered (referent)	1.0	1.0	1.0
HMO throughout	2.6 (0.9–7.2)	4.3 (1.2–15.4)	4.0 (1.01–16.3)
Other throughout	1.5 (0.5–4.4)	2.0 (0.6–7.1)	3.6 (0.9–14.2)
Mixed coverage	1.4 (0.5–4.4)	2.4 (0.6–8.8)	2.7 (0.6–11.2)
Baseline severity of asthma score	3.2 (2.0–5.1)	4.8 (2.7–8.7)	7.8 (3.4–15.2)
Baseline income‡	0.8 (0.8–1.1)	0.6 (0.5–0.8)	0.7 (0.6–0.96)

HMO = health maintenance organization.

*The logistic regression model also includes baseline age, sex, baseline SF-36 general health status (see text and Table 2 for description), education, atopic history, childhood asthma onset, history of ever-smoking cigarettes, and change in income at follow-up.
†The odds ratio (OR) for the severity score is expressed per 10-unit change.
‡The OR for income is expressed per $10,000 of per-adult family income.

In contrast, greater baseline asthma severity was a strong and consistent predictor of increased health services use. Lower baseline income and HMO insurance coverage throughout the follow-up (relative to lack of health insurance coverage) were associated with a statistically increased probability of emergency department visits and hospital admission.

Health Outcomes

The association between principal asthma care physician type and each of four measures of health and well-being outcome without adjustment for covariates is presented in Table 8. We further studied the predictors of asthma-specific quality of life, the SF-36 physical function score, the number of activity-restricted days, and the CES-D depression score using multiple-linear-regression analysis (Table 9). The overall explanatory power (R^2) of the models ranged from 0.19 for the CES-D score to 0.32 for the quality-of-life score.

When illness severity, income status, health insurance coverage, and demographic and clinical covariates were looked at, the group receiving their principal care from an allergy subspecialist reported poorer asthma-specific quality of life ($P = 0.02$) at follow-up than the group receiving their principal care from a pulmonary subspecialist. Adding to the model the baseline asthma-specific quality of life assessed at the initial interview did not appreciably change the parameter estimate for allergists' care ($\beta = 2.7$; $P = 0.03$).

Adding to the predictive model pneumococcal vaccination, PEFR-meter provision, high-dose inhaled-steroid use, and immunotherapy did not account for the

TABLE 8.—*Asthma-Related Health Care Outcomes by Principal Asthma Care Physician Type*

Outcome Measures	Principal Asthma Care Physician Type				P Value*
	Pulmonary (n = 283)	Allergy (n = 150)	Both (n = 53)	Neither (n = 53)	
Quality-of-life score†‡	20 ± 15	20 ± 14	20 ± 15	23 ± 15	>0.6
Physical function†§	71 ± 28	75 ± 23	68 ± 30	61 ± 30	0.01
CES-D depression score‖¶	5 (2–15)	4.5 (1–12)	6 (0–13)	10 (4–16)	0.03
Activity-restriction days‖#	0 (0–8)	0 (0–5)	1 (0–12)	2 (0–10)	>0.5

*Differences are tested by analysis of variance or the Kruskal-Wallis test.
†The scores are expressed as the mean ± standard deviation.
‡For the asthma-specific quality-of-life score, a higher score denotes poorer quality of life.
§For the physical function domain (see text and Table 2 for description), a higher score denotes better function.
‖The scores are expressed as the median (25% to 75%).
¶For the Center for Epidemiological Studies Depression (CES-D) score, a higher score denotes greater severity of depression.
#Denotes days of activity restricted because of health over past 30 days.

TABLE 9.—*Principal Asthma Care Physician Type and Asthma Outcomes: Multiple-Linear-Regression Analysis**

	Health Outcome Measure at 18-Mo Follow-up Interview							
	Asthma QOL Score† (Model R^2 = 0.30)		Physical Function‡ (Model R^2 = 0.32)		Restricted Days§ (Model R^2 = 0.21)		Depression Score‖ (Model R^2 = 0.19)	
Predictors of Outcome	β (SEM)	P	β (SEM)	P	β (SEM)	P	β (SEM)	P
Principal asthma care type								
Pulmonary (referent)	—		—		—		—	
Allergy	3.0 (1.3)	0.02	-1.5 (2.4)	0.5	-0.2 (0.9)	0.8	-0.4 (1.0)	0.7
Both	3.9 (1.9)	0.04	-9.1 (3.5)	0.01	3.0 (1.4)	0.03	0.4 (1.4)	0.8
Neither	2.7 (2.0)	0.2	-8.7 (3.6)	0.02	0.5 (1.4)	0.7	1.5 (1.5)	0.3
Baseline asthma severity	0.7 (0.1)	<0.001	-0.9 (0.2)	<0.001	0.3 (0.07)	<0.001	0.2 (0.08)	0.01
Baseline income¶	-0.6 (0.4)	0.14	2.9 (0.8)	<0.001	-0.7 (0.3)	0.04	-0.5 (0.3)	0.13
Follow-up income change¶	-1.2 (0.4)	0.005	2.8 (0.8)	<0.001	-0.9 (0.3)	0.002	-1.1 (0.3)	<0.001

SEM = standard error of the mean

*The multiple-linear-regression models also include age, sex, education, atopic history, childhood asthma onset, history of ever smoking cigarettes, and insurance status.
†For the asthma-specific quality-of-life (QOL) score, a higher score denotes poorer QOL.
‡The physical function domain (see text and Table 2 for description), a higher score denotes better function.
§The restricted days refers to the number of days of health-restricted activity over past 30 days.
‖The depression score refers to the Centers for Epidemiological Studies Depression scale; a higher score denotes a more severe depression.
¶The β coefficient for income variables is expressed per $10,000 of per-person adult family income.

association between allergy subspecialty follow-up and the overall quality-of-life score ($\beta = 2.6$; $P < 0.01$). Adjusting for the number of subjects initially recruited from the practice site also did not reduce the strength of this association. As shown in Table 9, allergists' care was not statistically associated with physical function, the number of restricted-activity days, or depression.

To further delineate the possible relationship between allergy subspecialist follow-up and subject-reported quality of life, we analyzed this relationship for each of the quality-of-life measures component subscores: breathlessness, mood disturbance, social functioning, and health concerns. When we took the same covariates listed in Table 9 into account, we found that allergy subspecialty follow-up was a significant predictor of poorer social functioning ($P = 0.03$) and greater health concerns ($P = 0.02$), but was less strongly associated with breathlessness ($P = 0.11$) or mood disturbance ($P > 0.2$).

Subjects who had changed their subspecialist type during follow-up reported worse quality of life, worse physical function, and more restricted-activity days than the group receiving care from a pulmonary subspecialist, taking into account the effects of all the other covariates included in the analysis (Table 9). The baseline asthma severity was a consistent predictor of poorer status assessed by each outcome measure. Greater baseline income and, more potently, increased income since baseline were associated with better health and well-being. None of the health insurance covariates (included in the model but not shown in Table 9) were statistically associated with any of the four outcome measures we studied.

Discussion

We identified several salient differences in practice and outcomes associated with the type of asthma care subspecialist. These differences, however, should be viewed in the context of the more consistent and powerful effects of underlying disease severity, insurance status, and income on health care use and asthma outcomes.

A notable practice difference related to the subspecialist group was in the dispensing of PEFR meters. The use of PEFR meters has been strongly promoted in guidelines for asthma management promulgated by the National Heart, Lung and Blood Institute, although its most recent expert panel report acknowledges that for mild disease, a symptom-based "action plan" may substitute for PEFR monitoring.[11,12] Subjects cared for by allergy specialists as their principal asthma care physician had nearly three times greater odds of having a PEFR meter than those subjects cared for by pulmonary subspecialists.

In contrast, the group receiving their principal care from an allergy specialist was a third as likely as the group being treated by a pulmonary specialist at follow-up to report using high-dose inhaled steroids (defined as ≥20 puffs per day), taking the baseline severity and a number of other covariates into account. This may reflect different subspecialty-related approaches to stepwise anti-inflammatory therapy in the pharmacologic management of asthma. Similarly, the pulmonary specialist-treated group was more likely to receive pneumococcal vaccination, taking into account the asthma-specific severity, including steroid use. Recent recommendations of the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention do not include nonsteroid-dependent asthma without concomitant chronic obstructive pulmonary disease or chronic bronchitis as a risk factor for pneumococcal pneumonia.[25] Although we excluded these comorbid diagnoses, limited the age of participants to 50 years and younger in our recruit-

ment, and included age and smoking history as covariates in our predictor modeling, we cannot exclude the possibility that the association between pulmonary practice and pneumococcal vaccination was confounded by such comorbidity.

The most salient outcome difference was in the quality-of-life measures. The group receiving their principal care from an allergy specialist reported poorer asthma-specific quality of life, even after a number of possibly confounding factors were adjusted for. The two subscale domains of quality of life accounting for most of this difference were those of social disruption and concerns of health. This should be put in context with the other health use and outcomes with which allergy-specific principal care was not significantly associated, including hospital admission, number of restricted-activity days, and impaired physical functioning. Nonetheless, National Heart, Lung and Blood Institute guidelines do emphasize that quality of life is one of the six principal domains of asthma health.

This is an observational study. We did not randomly assign patients to be treated by different subspecialists, nor did we control their access to other consultants. For this reason, it is all the more important that the associations we observed took into account many possibly confounding variables that could affect subspecialty choice, including asthma severity, health insurance, income, and demographic factors. We cannot exclude the possibility that other confounders that we did not study may have been responsible for some of the associations observed. For example, an underlying deterioration from baseline may have resulted in both changes in follow-up care between pulmonary and allergy subspecialists and in worse outcomes.

Although our study design provides a powerful, prospective comparison between pulmonary and allergy subspecialists, it cannot address the comparison between subspecialty and generalist care. All of our subjects, at a minimum, received a subspecialist consultation before study entry by the very nature of the subject recruitment design. Over the follow-up period, most received care by medical subspecialists who the subjects identified as their principal asthma care physicians.

We defined a group of 53 subjects who were not followed up closely by subspecialists, but this was a heterogeneous group, including those with ongoing consultation, nonsubspecialty care only, and no regular medical follow-up. Although we took this variable into account in our analyses, we nonetheless had little statistical power to directly examine the question of generalist relative to subspecialist care in this study. We are currently recruiting a supplemental panel of patients from outpatient family practice settings that may help better address the important question of generalist compared with subspecialist care. A recent cross-sectional study comparing allergist- with generalist-treated adults with asthma from a single staff-model HMO observed poorer functional status among the generalists' patients.[16] Pulmonary specialist-treated patients, however, were specifically excluded from that study. Other published reports have also found differences in outcomes between adults with asthma treated by allergy subspecialists and those treated by generalists, but none have compared allergists' care with that of pulmonary subspecialists.[13–15,17,18]

Our subspecialty principal asthma care groups were not "pure." We did classify separately the 53 subjects who switched the identity of their principal asthma care physician between allergy and pulmonary subspecialists, but even so, 5% of subjects in the allergy or pulmonary specialist-treated groups reported at least some cross-consultation. This explains why some patients even in the pulmonary specialist-treated group could report ongoing immunotherapy. Moreover, other subjects likely received differing subspecialty consultation or treatment before the study period. For example, altogether 101 (36%) of the pulmonary follow-up group reported ever having received immunotherapy injections at some time, even though few were being so treated currently. We view such "cross-contamination" as a strength of the study because it reflects the realities generalizable to standard practice. To the extent that it leads to a misclassification by the treatment group, it would tend to minimize rather than exaggerate observed differences, making the associations that we found more conservative estimates.

Our survey design is highly dependent on subject-elicited responses. These may be affected by recall bias or in other ways. This study limitation must be kept in mind when interpreting these findings. We did not independently verify reported income, health care services use, or actual possession of a PEFR meter. We did employ, however, validated survey research instruments such as the SF-36, the asthma-specific quality-of-life battery, and our asthma-severity scoring system. The last demonstrated its strong association with a wide variety of asthma treatment, health care use, and health outcome variables. Overall, the loss to follow-up was minimal, although some selection bias may have been introduced by preferential losses of younger men. The initial recruitment numbers varied by practice site, and that may have influenced the findings, although we took this into account in the key analysis of quality of life. Also, sex, age, and smoking did vary by asthma-care group. We included these covariates in the multivariate models we analyzed.

The differences in management, health care use, and outcomes we observed have a number of implications. The use of PEFR monitoring is particularly relevant to the implementation of asthma management guidelines. Health insurance and income status in relation to outcomes are central to health care policy. The quality of life in asthma, precisely because it is subjective, is becoming increasingly important as an outcome measure in this condition.[26] With the accrual of additional subject follow-up time, we intend to better delineate the relationships among these variables for adults with asthma to address these critical issues.

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Commentary

Respiratory Therapist–Driven Protocols

Rationale and Efficacy

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Therapist-driven protocols, also known as respiratory care– or patient-driven protocols, are prescribed plans for a specific respiratory care service that are implemented under respiratory care practitioners' supervision. The protocol is often a guideline or a branching-logic algorithm that is developed collaboratively by the medical director of respiratory care and respiratory care practitioners with the goal of assuring the appropriate allocation of these services.

As an extension of a single therapist-driven protocol, a respiratory therapy consult service, also known as an evaluate-and-treat program, is a program in which respiratory care is directed by respiratory care practitioners based on a menu of protocols for individual respiratory care services. Thus, in a respiratory therapy consult service, respiratory care practitioners bear the additional responsibility of applying sign- and symptom-based protocols to ascertain which services are needed and then implementing those services under protocol guidance. After initial therapy is implemented, protocols generally allow therapy to be titrated by either escalating or reducing the number and intensity of respiratory care services as patients' clinical needs dictate.

See Editorial, pages 440–441

As suggested by their widespread adoption and growing attention in the literature, therapist-driven protocols have attained widespread popularity. For example, a poll of 32 attendees at the 1994 American Association for Respiratory Care House of Delegates indicated that 13 (41%) were currently using therapist-driven protocols and 5 (16%) were planning their use. Similarly, a 1995 poll of respiratory care managers in the California Society of Respiratory Care showed that 50% were currently using protocols and 42% were planning to do so.

Therapist-driven protocols have been proposed as a way to improve the allocation of respiratory care services, and several lines of evidence suggest their efficacy in enhancing appropriate allocation. That a new strategy may help is suggested by the widespread misallocation of respiratory care services under the traditional, physician-directed approach to prescribing respiratory care. Table 1 summarizes the frequency with which respiratory care services have been misallocated—either prescribed when not likely to offer clinical benefit ("overordering") or not prescribed when indicated ("underordering").[1–6] As shown, rates of overordering for a variety of respiratory care services range from 32% to 72%, and the rates of underordering (which is less well-studied) range from 7% to 21%.

As further supportive evidence, a growing number of studies have shown that implementing therapist-driven protocols can lessen the misallocation of respiratory care services, thereby improving clinical outcomes and maintaining the cost of providing care. Such advantages of therapist-driven protocols have been demonstrated in a variety of clinical services. For example, in one study of intensive care units, it was shown that implementing appropriate guidelines for measuring arterial blood gas values lessened the rate of the inappropriate use of arterial blood gases from 43% to 33% and that respiratory care practitioners were far less likely than other health care professionals to measure arterial blood gases inappropriately (3% inappropriate rate versus 45%).[7] Another study showed that a therapist-driven protocol for weaning patients who have had open-heart operations from mechanical ventilation was associated with a slight decrease in the total duration of mechanical ventilation (mean, 18.6 to 16.8 hours) without adverse events (such as higher reintubation rate or higher rate of initial weaning failure).[8] Recently, a report of a randomized controlled trial of a therapist-directed weaning protocol in 357 patients showed that the rate of successful weaning was higher in the protocol-directed weaning group (relative risk, 1.31; $P < 0.04$).[9] Also, the duration of weaning was shorter (median, 35 versus 44 hours) and the hospital charges were lower (mean, $3,866 per patient) with no higher mortality in the protocol-directed group.

In non–intensive care unit inpatient care, favorable experience with therapist-driven protocols also supports their use.[10–12] For example, a review of respiratory care

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orders by respiratory care practitioners found that the volume of many respiratory care services was substantially reduced (up to 17%), with concomitant savings ($16.35 per patient).[12] In our experience with the Respiratory Therapy Consult Service at the Cleveland (Ohio) Clinic Foundation, implementing a protocol for titrating supplemental oxygen in postoperative patients substantially shortened the total duration of oxygen therapy and the number of pulse oximetry measurements, with concomitant cost savings of $21.73 per patient. Extrapolated to all adult inpatients receiving supplemental oxygen at our institution in 1995 (n = 12,119), the projected aggregate annual savings is $263,346. Finally, in a recently reported observational cohort study comparing respiratory care that was directed by the respiratory therapy service with that directed by physicians in 98 patients,[11] despite caring for sicker patients with longer lengths of stay and higher total hospital charges, the respiratory therapy service generated fewer inappropriate orders than physicians and provided a similar number of total respiratory treatments at slightly lower cost without any excess adverse respiratory events.

Therapist-driven protocols appear to be effective strategies for improving the allocation and provision of respiratory care services in the current cost-attentive era. Their implementation requires a committed and collaborative interaction among respiratory care practitioners, medical directors of respiratory care services, physicians, and nurses, as has been achieved in a growing number of institutions and settings.

TABLE 1.—*Frequency of the Misallocation of Respiratory Care Services in Selected Series**

Types of Service	*Patient Type*	*No. of Patients*	*Frequency of Overordering*	*Frequency of Underordering*
Supplemental oxygen				
Zibrak et al, 1986[1]	Adult	NS	55% reduction in incentive spirometry after therapist supervision begun	NA
Brougher et al, 1986[2]	Adult, non-ICU inpatients	77	38% ordered to receive oxygen despite adequate oxygenation	NA
Small et al, 1992[3]	Adult, non-ICU inpatients	47	72% of those checked had PaO_2 >60 mm of mercury or SaO_2 >90% but were prescribed oxygen	NA
Kester and Stoller, 1992[4]	Adult, non-ICU inpatients	230	25.2% overall for 5 respiratory care services; 28% for supplemental oxygen	10.5% overall for 5 respiratory care services, 8% for supplemental oxygen
Albin et al, 1992[5]	Adult, non-ICU inpatients	274	61% ordered to receive supplemental oxygen despite SaO_2 >92%	21% underordered, including 19% prescribed to receive inadequate oxygen flow rates
Bronchial hygiene techniques				
Zibrak et al, 1986[1]	Adult	NS	55% reduction in incentive spirometry after therapist supervision begun	NA
Shapiro et al, 1988[6]	Adult, non-ICU inpatients	3,400 evaluations	61% reduction of bronchial hygiene after system implemented	NA
Kester and Stoller, 1992[4]	Adult, non-ICU inpatients	230	32%	8%
Zibrak et al, 1986[1]	Adult	NS	50% reduction in aerosolized medication after therapist supervision begun	NA*
Kester and Stoller, 1992[4]	Adult, non-ICU inpatients	230	12%	12%
Intermittent positive pressure breathing (IPPB)				
Zibrak et al, 1986[1]	Adult	NS	92% reduction in IPPB after therapist supervision begun	NA
Kester and Stoller, 1992[4]	Adult, non-ICU inpatients	230	40%	6.7%
Arterial blood gases (ABGs)				
Browning et al, 1989[7]	SICU inpatients	724 ABGs	42.7% inappropriately ordered before guidelines implemented	NA

ICU = intensive care unit, NA = not assessed, PaO_2 = partial pressure of arterial oxygen, SaO_2 = saturation of arterial blood with oxygen, SICU = surgical intensive care unit.

*From Stoller.[10]

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Commentary

Withholding and Withdrawal of Life Support From Critically Ill Patients

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The withholding and withdrawal of life support are processes by which various medical interventions either are not given to or are taken away from patients with the expectation that they will die as a result. These processes are carried out in many medical settings, but are especially common in intensive care units (ICUs). Strictly speaking, all patients who die while receiving close medical attention in an ICU or elsewhere do so as a direct result of the withholding or withdrawal of life-sustaining therapy. This is either because a decision has been made not to resuscitate the patient in advance of decompensation or because vigorous resuscitation will not be provided indefinitely. It is this more deliberate form of withholding and withdrawal of life support from critically ill adults that I focus on in this article, in which I discuss the ethical, legal, and clinical aspects of limiting care and the question of how to resolve conflicts between patients and health care professionals regarding such limitations. My purpose in this article is to inform physicians and other practitioners about these issues and thereby assist them in better managing the deaths of patients who are unlikely to benefit from life-sustaining therapy.

Ethical Aspects of Withholding and Withdrawing Life Support

Physicians who care for critically ill adults and who are considering withholding or withdrawing life-support care can draw from several summaries of the ethical propriety of limiting care.[1–5] One of the most succinct group statements is the Consensus Report on the Ethics of Forgoing Life-sustaining Treatments in the Critically Ill, which was prepared by the Task Force on Ethics of the Society of Critical Care Medicine and published in 1990.[6] In this report, it was noted that it is ethically appropriate to withhold or withdraw therapy either because a patient or surrogate decides to forgo treatment or because a physician judges that the major goals of therapy are unachievable. A decision to withdraw a treatment should not be more problematic than a decision not to initiate a treatment, particularly because starting therapy may be necessary to adequately evaluate a patient's condition. Any treatment derives its medical justification from the benefits that a patient and physician hope to achieve by employing it. When the treatment has achieved those benefits or can no longer be expected to do so, it loses its justification and may be withdrawn.

The task force's consensus statement also noted that there are no intrinsic moral differences between categories of treatment, such as cardiopulmonary resuscitation (CPR), ventilatory support, medications such as vasopressors and antibiotics, and the provision of hydration and nutrition by artificial means. Each treatment should be considered from a patient's perspective in light of the overall benefit that it may offer and the burdens it may entail, as well as the professional duties that are involved. Because treatment choices must be considered in relation to a patient's overall condition, a treatment offering a reasonable expectation of physiological benefits may be withheld from terminally ill patients. Treatments that serve only to prolong the dying process should not be used, and indefinitely maintaining patients in a persistent vegetative state raises ethical concerns both for the dignity of the patient and for the inappropriate use of health care resources.

A basic provision of the consensus statement was that the wishes of an informed adult patient with decision-making capacity should be the primary consideration in almost all decisions regarding treatment. When a patient (or surrogate in the case of a patient who is incapable of making decisions) and a physician (and other members of the health care team) agree that therapy should be limited, it usually should be. Treatments rejected by a patient or surrogate generally should not be imposed by a physician. When a patient or surrogate requests therapy that a physician considers futile, the physician should clarify the goals of treatment with the patient and may accede to the patient's wishes. The physician is not ethically oblig-

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ABBREVIATIONS USED IN TEXT

CPR = cardiopulmonary resuscitation
DNR = do-not-resuscitate [orders]
ICU = intensive care unit

ated to provide therapy, however, and may elect to transfer the patient's care.

The Society of Critical Care Medicine's consensus report did not discuss situations in which patients or their surrogates disagree with physicians but care cannot be transferred. Nor did it describe the role of ethics committees in resolving conflicts or the place of health care institutions in developing policies regarding the withholding or withdrawal of futile care. Furthermore, presumably because of when it was written, the report did not deal with the issue of how the physician-patient relationship has been affected by the growth of managed care, cost containment, and concern with limited medical resources. In this regard, some physicians think that their traditional duty to individual patients increasingly is being compromised by the desire of health care organizations to restrict access to certain services, including those of uncertain benefit. An alternative view is that physicians properly should broaden their advocacy of individual patients with a proportioned advocacy whereby more patients can receive treatment by limiting the provision of nonbeneficial care to a few.

Legal Aspects of Withholding and Withdrawing Life Support

Physicians clearly are influenced by real or perceived legal requirements in their attitudes regarding the withholding or withdrawing of life support. A few of these requirements have come in the form of statutes in areas such as brain death and organ transplantation, but most have been expressed through case law. As a result, it is important to understand how in recent years the courts have underscored the right of patients to refuse treatment, affirmed the concept that human life is more than a biologic process that must be continued in all circumstances, defined how therapies may or may not benefit patients, argued against a distinction between the withholding and withdrawing of life support, established guidelines for limiting life-sustaining treatment, and approached the resolution of disagreements among physicians and patients or their surrogates.

The first major judicial decision regarding the withholding and withdrawing of life support occurred in the case of Karen Ann Quinlan (1976), in which the father of a girl who was in a persistent vegetative state petitioned the court to be appointed guardian with the power to remove her from mechanical ventilation.[7] The lower court denied the petition, but the New Jersey Supreme Court reversed the decision. In doing so, the court reasoned that patients generally would accept or refuse medical treatment on the basis of its ability to support sentient life over mere biologic existence. Having concluded that Ms Quinlan, if she had been capable of making decisions herself, would have forgone therapy that could only prolong biologic life but not sentient life, the court decided that her right to privacy would be abrogated if it prevented the exercise of that right on her behalf. The court, therefore, granted the father's petition, allowing him to exercise "substituted judgment" for his daughter, and stated that life support could be withdrawn if her physicians and a hospital ethics committee agreed that such support did not alter Ms Quinlan's underlying condition.

The case of *Barber v Superior Court* (1983) involved two California physicians who performed surgical closure of an ileostomy on a Mr Herbert, who subsequently suffered cardiopulmonary arrest.[8] Five days later, determining that his coma was irreversible and with the consent of his family, the physicians withdrew not only mechanical ventilation but also intravenous fluids and nutrition. Although the family found no fault with this at the time, the physicians were accused of murder by a district attorney. After the case was heard by several courts, the California Court of Appeals ruled that because the physicians had considered it medically futile to continue treatment because sentient life could not be restored, they had not failed to perform their duty. The court did not distinguish between removing mechanical ventilation or removing fluids or nutrition because all were interventions that could either benefit or burden. Finally, the court held that, without evidence of malevolence, family members are the proper surrogate for patients who cannot make decisions and that prior judicial approval is not necessary if surrogates and physicians decide to limit care.

The only case involving withholding and withdrawing of life support to be heard by the US Supreme Court was *Cruzan v Director, Missouri Department of Health* (1990).[9] This case involved Nancy Cruzan, a young woman in a persistent vegetative state who required tube feeding rather than mechanical ventilation. Believing that she would not want to live in such a state, her parents asked to have tube feedings discontinued and were authorized to do so by a trial judge in Missouri. The Missouri Supreme Court reversed this decision, however, arguing that no one could exercise Ms Cruzan's right to refuse treatment on her behalf. The court also said that because the state had an interest in preserving life regardless of its quality, support could be terminated only if it could be shown by "clear and convincing evidence" that Ms Cruzan had rejected such treatment. The US Supreme Court, although acknowledging that patients had a constitutional right to refuse any form of life-sustaining treatment, also concluded that the constitution did not prohibit Missouri or other states from requiring evidence of a patient's wishes regarding life support. The Court did not require that other states follow Missouri's lead, however, and its decision does not affect the laws, ethical principles, or clinical practices elsewhere. In effect, the decision highlighted the desirability of all persons filling out advance directives,

including living wills and durable powers of attorney for health care, to facilitate medical decision making if and when they become critically ill.

The case of Helen Wanglie (1991) involved an 85-year-old woman who had a cardiopulmonary arrest during an attempt at weaning from mechanical ventilation at a long-term-care facility.[10] She was returned to Hennepin County Medical Center (Minneapolis, Minnesota) in a persistent vegetative state. Mrs Wanglie's physician recommended to her husband and children that life-sustaining therapy be withdrawn, but the family insisted that therapy be continued because they valued biologic life. Eventually a new physician told the family that he did not wish to continue mechanical ventilation because it was not beneficial as it could not heal Mrs Wanglie's lungs or end her unconsciousness; because mechanical ventilation could prolong life, it was not described as being physiologically futile. After the family tried and failed to find another facility willing to care for the patient, the medical center asked the district court first to appoint a conservator other than Mr Wanglie to decide if ventilation was beneficial and, second, for a hearing to determine whether ventilation was required if the conservator held that it was not beneficial. The court refused to replace Mr Wanglie on the grounds that he could best represent his wife's interests. Because Mr Wanglie died before a hearing could be held, the issues of whether ventilation was beneficial and whether physicians could override family wishes were not resolved.

The most recent case to explore the issue of whether physicians can override family wishes involved a 72-year-old woman named Catherine Gilgunn who was being cared for at Massachusetts General Hospital (Boston).[11] Mrs Gilgunn was comatose with irreversible brain damage and had congestive heart failure and gastrointestinal bleeding. Although Mrs Gilgunn's husband and two of her daughters agreed to physician recommendations for a do-not-resuscitate (DNR) order, another daughter disagreed, and the DNR order was discontinued. At a subsequent meeting to discuss the DNR order, this daughter stormed out without confronting the issue. The other two daughters agreed to reinstate the DNR order, and Mrs Gilgunn was removed from the ventilator. The daughter who had refused the DNR order brought action against her mother's physicians and the hospital. Subsequently, the jury in Suffolk Superior Court absolved the physicians and hospital of liability, apparently because they believed that further care was futile despite the possibility that Mrs Gilgunn might have wanted to be kept alive. Thus, for the first time, a US jury has determined that life-sustaining therapy may be discontinued despite the objections of a patient or his or her surrogate.

Clinical Aspects of Withholding and Withdrawing Life Support

Information about the clinical aspects of withholding and withdrawing life support has come primarily from surveys of physicians and other health professionals and from observational studies of the limiting of life-sustaining care. For example, several surveys[12–14] have suggested that the great majority of critical care physicians have withheld or withdrawn life support at one time or another and that many have done so frequently. Similarly, retrospective studies have found that about half the patients who die in ICUs do so during the withholding or withdrawing of life-sustaining therapy.[15–17] Prospective studies conducted in two ICUs in hospitals affiliated with the University of California, San Francisco, revealed that the withholding and withdrawal of life support preceded 90% of deaths in 1992 and 1993, compared with 51% of deaths in 1988 and 1989.[18,19]

To determine whether limiting care is as commonplace as suggested by the aforementioned studies, a prospective survey was conducted in 1994 and 1995 of 167 ICUs associated with all US training programs in critical care medicine or pulmonary and critical care medicine.[20] Data from 6,110 deaths of 71,513 admissions (8.5% mortality) in the 107 sites responding to the survey revealed that 1,517 (25%) deaths followed full ICU care and failed CPR; 1,407 (23%) deaths occurred in patients who received full ICU care excluding attempted resuscitation; 768 patients (13%) had some form of life support withheld before death; 2,032 (33%) deaths followed the withdrawal of life support; and 386 (6%) patients were brain-dead and had therapy withdrawn, in some cases after their organs were transplanted. If patients who did not receive CPR, who had life support withheld or withdrawn, and who were brain-dead are considered as a group, 75% of the patients in this study had treatment limited in some manner. This suggests that withholding and withdrawing life support are now common practice in most American ICUs.

Despite the fact that life support was commonly withheld or withdrawn in this study, substantial variability was noted among ICUs with regard to mortality (from 2% to 45%), failed CPR (from 4% to 79% of deaths), and willingness to withdraw life support (from 6% to 71%). Clearly, considerable heterogeneity exists in the processes of withholding and withdrawing life-sustaining treatment within the United States. Presumably this heterogeneity also occurs on an international basis, although this issue has not been explored from a research standpoint. Because of the heterogeneity, there is no precise standard of care in the practice of withholding and withdrawing life support, even though the practice is more common than ever before.

Most surveys[12–14,21] and studies[15–19,21,22] have indicated that physicians recommend that life support be withheld or withdrawn either because patients or surrogates request this action or because physicians think that further care is futile. Physicians vary in their definitions of futility, but the term generally conveys the ideas that a patient cannot benefit from treatment, that the patient's acute disorder is not reversible, that the patient will not survive the current hospital stay, or that the quality of the

patient's life following discharge will be poor. These ideas clearly stem from prognostication on the physicians' part. They generally arrive at estimates of prognosis through their personal experience and knowledge of the medical literature, although prognostic scoring systems such as the Acute Physiology and Chronic Health Evaluation system are used in some ICUs. If present, persistent coma, other unacceptable neurologic prognoses, and multiple organ system failure are important rationales for withdrawing care. The need for ICU beds, patients' social worth, and financial cost-benefit analyses are not important rationales.

Most patients have not prepared medical directives in advance of suffering a critical illness, and most patients are too neurologically depressed by their disease or by therapeutic drugs to make medical decisions when they become critically ill. Surrogates were available and willing to take part in the decision-making process in the prospective studies of withholding and withdrawing life support.[18,19] When surrogates were not available, physicians were willing to make decisions for the patients. Although consultation from other physicians often was sought before deciding to limit care, hospital ethics committees were infrequently involved.

The surrogates that were available in these studies either recommended by themselves that support be withheld or withdrawn when patients were not improving or accepted physicians' recommendations to that effect.[18,19] These recommendations were not always accepted immediately, but in most cases, the surrogates agreed within a few days. Only rarely did surrogates insist on continued care against the advice of physicians, and in all cases, care was continued. In certain instances, however, the physicians stopped short of providing CPR in patients who were otherwise supported.

Although differences between physicians and surrogates do occur over the issue of limiting care, their incidence is uncertain. In a survey of self-identified members of the critical care section of the American Thoracic Society, 34% of respondents reported that they had refused surrogate requests to withdraw care either because they thought that the patient had a reasonable chance of recovery or that the surrogates might not be acting in the best interest of the patient.[13] At the same time, 83% of physicians reported that they had unilaterally withheld life-sustaining treatment on the basis of futility, often without patient or surrogate knowledge or consent, and 82% had withdrawn treatment on the same basis.

Cardiopulmonary resuscitation probably is the therapy most often withheld from ICU patients, as suggested by the finding that DNR orders preceded 60% of all in-unit deaths between 1980 and 1990 in a large observational study[23] in 40 US hospitals compared with only 39% of all in-unit deaths from 1979 to 1982 in a similar study.[24] Antibiotics, vasoactive drugs, renal dialysis, and mechanical ventilation were commonly withheld in the two studies from ICUs in hospitals affiliated with the University of California, San Francisco.[18,19] Mechanical ventilation was the therapy most commonly withdrawn in these studies, followed by the use of vasoactive drugs. In the survey of American Thoracic Society members,[13] 89% of the respondents had withdrawn mechanical ventilation, 88% had withdrawn vasoactive drugs, and 80% had stopped administering blood or blood products.

A survey of randomly selected US members of the Society of Critical Care Medicine in 1991 and 1992 revealed that 15% of respondents almost never withdrew mechanical ventilators from patients who were expected to die, 15% almost always did so, and the remainder withdrew ventilators some or most of the time.[25] Of physicians who withdrew ventilators, 33% preferred the gradual withdrawal of supplemental oxygen and positive end-expiratory pressure treatment before removing the ventilator, a process called terminal weaning[26]; 13% preferred rapid extubation; and the remainder used both methods. Reasons for preferring terminal weaning included patient comfort (65%), family perceptions (63%), and the belief that terminal weaning was less active (49%). Reasons for preferring extubation included the directness of the action (72%), family perceptions (34%), and patient comfort (34%).

In this survey of Society of Critical Care Medicine members,[25] morphine sulfate and other opiate analgesics were used by 74% and diazepam and other benzodiazepines by 53% of physicians who withdrew ventilators; 6% used muscle relaxants at least occasionally. In a study conducted in 1988 and 1989 in the two ICUs at hospitals affiliated with the University of California, San Francisco,[27] analgesics and sedatives were given to 75% of non–brain-dead patients during the withholding and withdrawal of life support. Patients who did not receive medication were comatose and considered incapable of benefiting from the drugs. Physicians ordered analgesics and sedatives to decrease pain in 88% of patients, to decrease anxiety in 85%, to comfort families in 82%, to decrease air hunger in 76%, and to hasten death in 39%; in no instance was hastening death the only reason cited. The amounts of opiates and benzodiazepines averaged 3.3 mg per hour of morphine and 2.2 mg per hour of diazepam in the 24 hours before withholding and withdrawing life support and 11.2 mg per hour and 9.8 mg per hour, respectively, in the 24 hours thereafter. The median time until death following the initiation of withholding and withdrawing life support was 3.5 hours in the patients who received drugs and 1.3 hours in those patients who did not. Thus, the administration of sedatives and analgesics did not appear to hasten death in this study.

It would appear from these surveys and studies that the withholding and withdrawal of life support from adults occurs frequently in most ICUs in the United States and that these processes commonly follow a similar course. Furthermore, professional attitudes and behaviors on the part of physicians are consistent with ethical pronouncements and judicial decisions regarding the withholding and withdrawing of life support. The only major area in which consistency may be lacking

concerns physicians' refusal to follow surrogate demands either to limit care in certain circumstances or, more commonly, to provide care that the physicians consider futile. This finding is not surprising given the lack of legal clarification of the issue and the frequent conflicts over ethical principles such as patient autonomy and distributive justice in ICUs.[27,28]

Resolving Conflicts Between Patients and Health Care Professionals

Although physicians' refusal to provide care has not been legally clarified, the medical profession cannot wait for case law to develop before defining its own values and describing methods for resolving conflicts between patients and their physicians. The Ethics Committee of the Society of Critical Care Medicine recently developed a Consensus Statement Regarding Futile and Other Possibly Inadvisable Treatments to assist in such a resolution.[29] Because of the wide variation in physician definitions of futility, the ethics committee decided to define as futile only those treatments that cannot accomplish their intended physiological goal. Treatments that are extremely unlikely to be beneficial, are extremely costly, or are of uncertain benefit they considered inappropriate and hence inadvisable.

Because futile treatments constitute a small fraction of medical care according to the definition of the aforementioned ethics committee, employing the concept of futile care in decision making will not help reduce the use of ICU resources. Nevertheless, society has a legitimate interest in allocating medical resources wisely by limiting inadvisable therapies. Communities should seek to do so by using a rationale that is explicit, equitable, and democratic. Policies to limit inadvisable treatment—which are called futility policies by other groups concerned with medical ethics—should have the following characteristics:

- Be disclosed in the public record,
- Reflect acceptable moral values,
- Not be based exclusively on prognostic scoring systems,
- Contain appellate mechanisms, and
- Be recognized by the courts.

Health care organizations that control payment or services or both should formally address criteria for determining when critical care treatments are inadvisable, and their policies regarding such treatments should contain the characteristics just described.

Although physicians do not have a responsibility to provide futile or inadvisable care,[30] they should not withhold or withdraw life support based solely on their research notions of futility, but instead should rely on institutional or multi-institutional policies.[31] Such a policy has been developed by representatives of major hospitals in Houston, Texas.[32] Under that policy, when a physician determines that an intervention is inadvisable but a patient or surrogate insists that it be provided, the physician first must discuss the reason for his or her judgment, the possibility of transferring care without abandoning the patient, and alternative treatments such as palliative care. If agreement is not reached at this point, the physician must obtain a second opinion from another physician who has examined the patient and must present the case before an institutional review body. If the review body affirms that a treatment is inappropriate, the treatment is terminated, a plan for alternative care is established, and intrainstitutional transfer to another physician to provide the treatment that has been deemed inadvisable is not allowed. On the other hand, if the review body finds that the intervention is appropriate, orders to terminate the treatment are not recognized as valid without patient or surrogate assent.

The Houston Collaborative policy is limited in that it was developed by institutional representatives without explicit community involvement. The legal standing of the policy remains uncertain, and it is not clear whether the policy is workable in ICUs or that physicians will follow it rather than openly or surreptitiously limiting care on their own. Nevertheless, the policy represents a commendable approach in balancing patient autonomy and professional and institutional integrity, and its presence seems to have prompted dispute resolution before institutional review bodies are required. Ideally, policies such as this should move society closer to a consensus on which treatments are truly beneficial and how limited resources should be allocated.

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Mad Cow Disease

An Opportunity for Preventive Medicine?

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Cost considerations are being increasingly employed as a basis for health care decisions. Formal cost-effectiveness analysis explicitly attempts to compare different treatment or prevention strategies based on both cost and effectiveness differences. By this manner, cost-effectiveness analysis provides decision makers with valuable data for making important and difficult decisions about interventions.[1] "Back of the envelope" strategies can also aid in decision making by providing general information about the relative differences of various interventions.[2]

The recent occurrence of a serious but rare neurologic disease in Great Britain offered another potential role for cost analysis. In this instance, a relatively simple analysis leads to information with major implications for public policy. The disorder in question is the "mad cow disease," or bovine spongiform encephalopathy (BSE). Widespread anxiety was generated when officials made public a possible association between BSE and human variant Creutzfeldt-Jakob disease (CJD; vCJD).[3] Both dementing disorders may be caused by prions.[4] Because of the common features of the two conditions, it is speculated that vCJD may have been contracted by ingesting beef from cattle with BSE.[5] Indeed, ten human cases of vCJD were reported as of April 1996.[3] Though a rare disease, its serious nature and possible linkage to dietary habits of the entire English population rendered necessary a governmental policy to address public health and fears.[5,6]

Options considered by the British government and health officials included the following:

- Immediately killing all British cattle, both young and old;
- Destroying the carcasses of older dairy cows as they come up for slaughter (rather than selling this beef as low-grade meat); and
- Continuing the current system of processing older dairy cows as low-grade meat.

Given that BSE is a disease of cattle older than 30 months and that the incidence of BSE in cows born after 1993 is low (because of dietary precautions instituted on farms in the late 1980s),[7,8] we postulated that killing younger cows in addition to older cows would do little to prevent the spread of vCJD. Older cows (born before 1993) may, however, present a risk to humans.

We performed a back-of-the-envelope analysis[2] comparing three strategies. In the first, the entire British herd is immediately slaughtered and BSE is eradicated. As a ten-year incubation between exposure to BSE and the development of vCJD is postulated, six new cases of vCJD would still be expected to develop yearly for another decade. In the second scenario, the carcasses of older cows are destroyed. Because this strategy prevents people from eating older cows, we assumed it would be effective (95% for the purposes of this analysis) in halting the spread of BSE. The incidence of vCJD would therefore decrease by 95% after the ten-year latency period. Finally, some think that all cattle will be disease-free in six years (again, because of dietary changes instituted on farms in the late 1980s). Therefore, even if the British government continues to allow the human consumption of older cattle, vCJD will remain a public health problem for only another 16 years. The human consequences of these strategies are presented in Table 1.

By this analysis, destroying older dairy cows rather than consuming them would prevent about 57 cases of vCJD over six years. Because reported cases of vCJD occurred in adults with an average age of 26 years, about 50 years of life expectancy would be lost with each premature death due to vCJD. Therefore, a total human cost of 57 lives times 50 years per life, or 2,850 years of life, might be lost to vCJD if nothing were done. The possible cost of destroying the older cows has been estimated at $1 billion.[9] Therefore, the cost-effectiveness ratio ($1 billion ÷ 2,850 years) of destroying older cows is about $350,000 per year of life saved.

(Salzmann P, Saint S, Tierney LM Jr. Mad cow disease—an opportunity for preventive medicine? West J Med 1997; 167:417–419)

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ABBREVIATIONS USED IN TEXT

BSE = bovine spongiform encephalopathy
CJD = Creutzfeldt-Jakob disease
vCJD = variant CJD

Our incidence assumption is based on ten cases reported by the CJD surveillance unit divided by the at-risk British population. What if the CJD surveillance unit only identified the tip of the iceberg? If vCJD is more prevalent, its effect will be greater. Because tissue is required for a definitive diagnosis and because the disease is uncommon with unusual manifestations, it is possible that many cases were missed. Alternatively, the incidence of vCJD might rise in the future, just as the incidence of BSE increased in the early 1980s. If the actual incidence of vCJD is three times higher than currently reported, then the data in Table 2 apply.

In this case, destroying older cows might save 8,550 years of life (171 lives × 50 years per life). The cost-effectiveness ratio would then fall to about $120,000 per year of life saved. In general, public health programs are considered attractive if their cost-effectiveness ratio is less than $40,000.[10] Many widely practiced therapies (the use of nonionic radiographic contrast material, drug therapy for hypercholesterolemia, or warfarin sodium instead of aspirin for nonvalvular atrial fibrillation when other risk factors for stroke are absent)[11–13], however, have cost-effectiveness ratios closer to $150,000 per year of life saved. Whether society can afford to fund such programs is often debated. In any case, our simple analysis suggests that destroying older cows may be at least as cost-effective as some common medical interventions.

Should the entire herd be slaughtered and the problem potentially solved? In fact, some advocate slaying all British cattle. This additional effort would probably save only a few additional lives. Even when vCJD is assumed to be more prevalent (as in Table 2), killing all the cows only saves an additional 450 years of life (9 additional lives × 50 years per life). Furthermore, this annihilation would be expensive, perhaps $1 billion more than simply destroying the older cows. Therefore, the cost per additional year of life saved for this aggressive strategy is about $4.5 million ($2 billion ÷ 450 years of life) based on our assumptions. Most would agree that this strategy is unusually expensive. Even if the numbers used in our analysis are somewhat off, the conclusion will likely be similar: targeting the high-risk reservoir (older cows) is expensive because vCJD is rare and the reservoir is large. Nevertheless, many public health interventions are similarly expensive. On the other hand, a policy designed to eradicate the problem by targeting all possible reservoirs would cost far more than currently recommended public health programs because the marginal benefit of this tremendous effort would be small.

Money is not the only issue. Many think that the heart and soul of Britain are symbolized by beef. Beginning with the American Revolution, through the loss of India, and with the current debate over the future of its monarchy, British pride and sense of self-worth are in a precarious state. If not for the stability of British beef over the years, symbolic of the heartiness and resiliency of the land itself, the British people would have strongly considered emigrating en masse to France long ago. Thus, it is no trivial matter that trust in British beef be restored as soon as possible.

TABLE 1.—*Number of Human Cases of Variant Creutzfeldt-Jakob Disease (vCJD) Based on Each of 3 Strategies*

Strategy	*Cases of vCJD in Next 10 yr, No.*	*Cases of vCJD in Years 11–16, No.*
Kill all cows	100	0
Destroy older cows	100	3
Eat the beef	100	60

Our simplified cost-effectiveness analysis has several limitations. Neither the precise incidence of vCJD nor the efficacy of destroying older cows to prevent the disease is known. Furthermore, although our cost data are based on published estimates, they are not precise. Nevertheless, the British government has to act quickly, even though a complete understanding of the relationship between BSE and vCJD may be decades away. One of the strengths of cost-effectiveness analysis is to highlight which strategies are possibly reasonable when incomplete data preclude a definitive answer.

If the United States is faced with a decision similar to that faced by the British, notwithstanding current evidence that no American cases of vCJD have occurred,[14,15] policy makers in this country may also have to act on less than optimal data. Fortunately, we have not seen a BSE epidemic, perhaps for the following reasons: First, the strains of the related sheep disease (called scrapie) in the United States differ sufficiently from those seen in Great Britain and, thus, may not breech the species barrier to cattle.[16] Second, the level of infectivity in the United States may be sufficiently low as to prevent transmitting disease from sheep to cattle.[16] Furthermore, several precautionary steps have already been taken in the United States, including embargoing the importation of cattle from Great Britain, restricting

TABLE 2.—*Number of Human Cases of Variant Creutzfeldt-Jakob Disease (vCJD) Based on Each Strategy if the Actual Incidence of vCJD Were Increased 3-fold*

Strategy	*Cases of vCJD in Next 10 yr, No.*	*Cases of vCJD in Years 11–16, No.*
Kill all cows	300	0
Destroy older cows	300	9
Eat the beef	300	180

the movement of scrapie-infected sheep into uninfected flocks, and providing incentives to the sheep farming industry to reduce the incidence of scrapie in the United States.[16]

Fear is a powerful emotion. Some British government officials have implied that the public's fear is without scientific basis and that the response to mad cow disease has been hysterical.[17] But a lack of proof of a direct association does not prove there is no association.[18] As long as the British public believes that the new cases of vCJD may be associated with BSE, then it is not unreasonable for the British government to act on this belief and to pursue a strategy of destroying older cows.

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Special Report

The Future of Veterans Affairs Medical Centers

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This article is based on a paper presented at the 42nd annual meeting of the Western Association of Physicians, Carmel, California, February 6, 1997.

In the past four years, the Department of Veterans Affairs (VA) has experienced unprecedented changes in the ways it provides medical care, trains medical residents, and supports its clinical research program. For the most part, these changes have improved the quality and efficiency of care provided to veterans, and they have improved the chances that the VA will survive in an increasingly competitive medical market place. While the changes in priorities for training medical residents and funding clinical research have been designed to be more consistent with the overall mission of the VA, these changes have been stressful for many of the VA/medical school affiliations. Our challenge is to understand and manage these changes so that the many benefits that have derived from more than fifty years of VA/medical school affiliations can be retained.

(Smith CB. The future of Veterans Affairs medical centers. West J Med 1997; 167:420–425)

Strong partnerships have developed over the past 50 years between the Department of Veteran Affairs medical centers and medical schools. Anxieties are widely expressed about the future of academic medical centers and the ability of the VA to support the high standards in medical education, research, and clinical practice that are the foundations of this organization. These anxieties are in response to two major sociopolitical forces: the bipartisan political support for balancing the federal budget and the social, political, and marketplace demands that the VA reconsider its priorities and structures for providing health care, medical education, and research. In this report, I focus on these two issues, the future for funding of the VA and the tremendous changes that the VA is attempting to make in its organizational structure to meet the challenges of an increasingly competitive medical marketplace.

Funding for the Department of Veterans Affairs

The VA health care budget has increased at an average rate of about 4% per year for the past four years (Figure 1). Although this increase has not kept up with inflation in medical costs during this period, it reflects a remarkably good level of bipartisan support for VA health care given the conservative nature of the past two Congresses and the large budget reductions that were handed the US Department of Defense and some other federal agencies during this time. Our immediate concern is with the strengthening alliance between Congress and the Clinton Administration in planning for a balanced federal budget by 2002. The president's current proposed budget for VA health care in fiscal year 1998 through 2002 is for a flat budget in terms of appropriations, which would soon lead to reductions in services provided by the VA as medical inflation eats away at purchasing power. To compensate for this, the president has asked for legislation allowing the VA to increase its ability to collect and retain nonappropriated funds, with the expectation that at least 10% of the VA budget will come from nonappropriated funds by 2002. The VA currently bills third-party insurers for care provided to insured veterans; most of these collections, however, are now deposited in the federal treasury, and the Clinton Administration proposed that all of these proceeds (approximately $600 million) be retained by the VA. In addition, the administration is asking for legislation to permit it to test the feasibility of the VA becoming a Medicare provider for veterans who are eligible for Medicare but not for VA care because their incomes exceed the means-test threshold of approximately $21,000 per year for a single veteran. This request to stake the future of VA health care in part on nonappropriated "soft money" has understandably created some anxieties among veterans service organizations. They fear that it is the beginning of a change where Congress

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ABBREVIATIONS USED IN TEXT
VA = [Department of] Veterans Affairs
VISN = Veterans Integrated Service Network

can diminish its long-accepted responsibility to care for those who bore the wounds of war. At the time of this presentation, debate over these proposals for new funding streams for VA is in full sway and will likely continue through the end of the current fiscal year.

This major change from total dependence on federal appropriations to an acceptance of the risks associated with competing for private and possible Medicare reimbursements underlies the pressures on the VA to reconsider its priorities and management structures with the goal of becoming more efficient. In support of the request to Congress for permission to accept nonappropriated funds, VA's strategic plan is to reduce the average cost of care per patient by 30% and to increase by 20% the total number of veterans cared for by 2002. Some will be doubtful that a federal agency this large and traditionally politically micromanaged and bureaucratic can make the changes necessary to achieve these goals.

In fact, evidence gained over the past four years suggests that the VA is in the midst of changes that are unprecedented in a federal agency of this size and complexity.[1] As part of the widespread assessment of our national health care system initiated by the Clinton Administration and the specific charge to federal agencies from Vice President Gore to "reinvent government,"[2] in 1994 the VA started the reinvention process by convening task forces and advisory groups from the field. In the initial product of these deliberations, *Vision for Change*, the Undersecretary for Health Kenneth Kizer proposed a restructuring whereby the vision, mission, and overall strategic plan for the VA would be strengthened and depoliticized at the central or "headquarters" level and most responsibility and authority for operational decision making would be moved to the field. In the subsequent document, *Prescription for Change*,[4] the new structure was further defined, and for the first time, specific performance expectations of VA network and medical center leaders were described. The new structure moved most of the resources and operational decision authority to the directors of 22 newly created regional networks or Veterans Integrated Service Networks (VISNs). These networks were designed around natural patient referral patterns, and the emphasis in funding and planning was to support an increased provision of integrated health care to the entire population of veterans in the network. This represented a dramatic change from the old system in which most health care planning and funding was directed at individual medical centers, and providing episodic tertiary care services to individual patients often took precedence over integrating health services for populations of patients. Although support for the decentralization of operational authority from

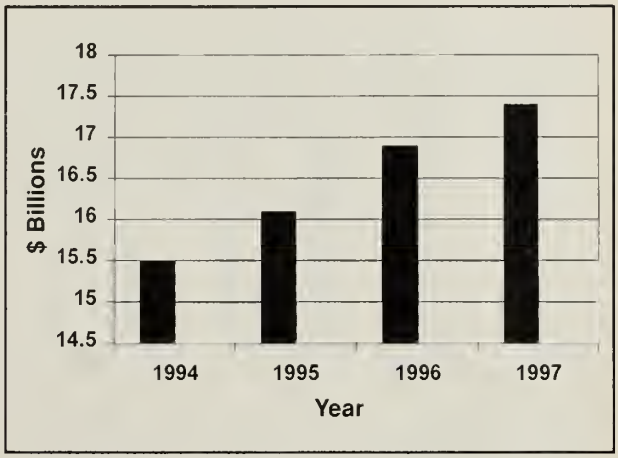

Figure 1.—The Department of Veterans Affairs medical care budget (in billions of dollars) from 1994 to 1997.

Washington, DC, to the "field" has generally been widespread, individual medical centers have lost some autonomy, and VA academic medical centers and their affiliated medical schools are currently in the throes of adjusting to the new priorities and organizational structure.

The funding of individual VA medical centers has for many decades been inappropriately influenced by congressional pork-barrel politics, and an important component of the new VA vision has been an emphasis on redistributing resources according to workload and need rather than political influence. This was considered to be a critical first step toward having VA medical center leaders become more accountable for the quality and cost of care. A comparison of the annual cost of caring for patients in dollars per patient per year, or in physician fulltime-equivalent units per patient per year, reveals more than a 70% variation between VISNs across the country (Table 1). In general, the VISNs in the Northeast are among the most expensive, and those in the West are among the least expensive. This difference reflects in part the decline in veteran patient populations in the Northeast and their growth in the West, but it also reflects differences in clinical practice patterns and cost per unit of care between these two areas of the country that have been observed by the Healthcare Financing Administration in Medicare billings and by studies of small area variations.[5] The Veterans Equitable Resource Allocation model for the distribution of resources among VISNs and medical centers is designed to reward the tighter management of costs per patient and is thus a capitated system that provides $2,600 per patient for basic care and $36,000 per patient for high-cost special care, such as spinal cord injury and chronic mental illness. With the use of this model in the fiscal year just past (October 1996 through September 1997), the process of decreasing the funding for inefficient medical centers and increasing funding for efficient centers has begun, with some of the western VISNs receiving more than a 6% increase in funding (Table 2). If the rationality of this redistribution system can surmount the expect-

TABLE 1.—*Variance From the Mean Cost of Providing Care Among Selected Veterans Integrated Services Networks (VISNs) in 1995 in Annual Dollars Spent and Numbers of Fulltime-Equivalent Physicians per Patient Seen*

VISN	%Δ Annual Cost/Patient	%Δ FTE Physician/Patient
Bronx, NY	+36	+45
Chicago	+25	+25
Boston	+16	+20
Long Beach, CA	+8	+18
San Francisco	−2	+8
Denver	−12	−15
Portland, OR	−10	−20
Phoenix	−36	−34

TABLE 2.—*Projected Effects of Veterans Equitable Resource Allocation (VERA) Model on Percent Change (%Δ) in Veterans Integrated Services Network (VISN) Budgets, 1996 to 1999*

VISN	%Δ 1996–1997	%Δ 1996–1999
Bronx, NY	−1.16	−14.9
Chicago	−1.05	−7.1
Boston	−1.26	−6.4
Long Beach, CA	+1.93	+1.28
San Francisco	+4.70	+6.21
Denver	+4.75	+6.60
Portland, OR	+6.09	+15.0
Phoenix	+6.90	+16.0

ed protests from congressional representatives in the losing states, the proposed changes needed to achieve equitable funding in the VA system are considerable, and they should generally favor the cost-effective VISNs.

Because the VA is requesting legislation that would permit it to compete in the Medicare market for veterans who are Medicare-insured but who are not eligible for VA care because their income exceeds the means-test threshold, the question should be raised about the likelihood that the VA can compete on cost and quality of care. Although the ability of VA medical centers to measure costs of episodes of care is not well developed, it is possible to compare the costs of care given to defined populations of veterans with those of community standards. In 1994 the Northwest VISN contracted with the Milliman and Robertson health care accounting firm to compare the VA costs per patient per year with those of the Northwest medical marketplace. After matching the populations for age and sex, the overall VA cost per patient per year of $3,700 was similar to the calculated non-VA community charges of $3,800 for the usual commercial health care package. The VA, however, generally provides a richer package of benefits, especially in the breadth of psychiatric and rehabilitation services, and the adjusted cost for a community package of the VA benefits would have been $4,100, or about 10% more than the calculated VA costs. The health care playing field is constantly changing, however, and the comparison is not as favorable toward the VA when the accountants considered an aggressive managed care competitor who was projected to charge only $3,300 per patient per year, a competitive edge of 10% over the VA. The Northwest VISN in 1994 was, therefore, competitive with the current marketplace in terms of cost, but the rapid changes toward a more competitive managed care marketplace in the Northwest would have left the VA behind if it had not taken measures to provide more cost-effective care. Certainly those VISNs that are expensive by VA measurements will need to make greater changes to become cost-effective.

Systemwide trends in the VA since 1994 indicate that dramatic changes are occurring in acute-bed-use measures that may correlate with efficiency in providing care. Traditionally, the VA funded medical centers according to bed-days of care, and not surprisingly, hospital managers kept the beds full. Admissions for care that could have been provided in the ambulatory setting and the subsequent lengths of stay for common conditions widely exceeded those of community hospitals.[6] Substantial declines in the number of admissions, and particularly in the number of bed-days of care, have occurred since 1994 (Figure 2).

These reductions in expensive, and often unnecessary, inpatient care days have been associated with increases from 1994 to 1996 in ambulatory clinic visits (19%), the percentage of patients assigned a primary care physician (72%), provisions of clinic visits within 30 days (79%), and in the percentage of surgical procedures done in the ambulatory setting (52%) (Figure 3). If these trends continue, it is likely that Under Secretary Kizer's plan that the VA will decrease by 30% the average cost of care per patient by 2002 will be achieved before that date. In this area, Congress has been an ally with the VA in passing eligibility reform legislation last year that eradicated old regulations that forced veterans into acute hospital beds before they could become eligi-

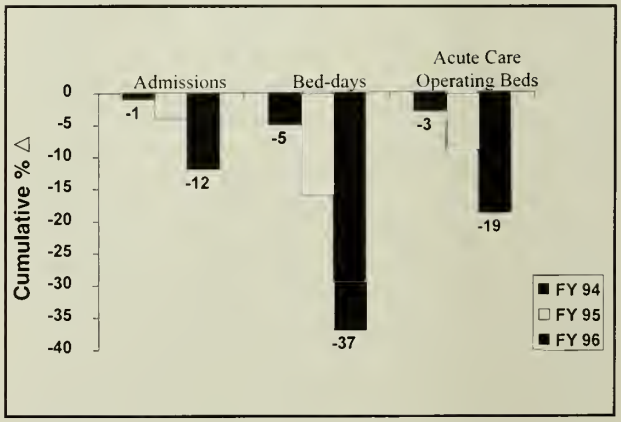

Figure 2.—Cumulative percent changes are shown in Veterans Affairs medical centers admissions, bed-days of care, and number of acute operating beds from 1994 to 1996.

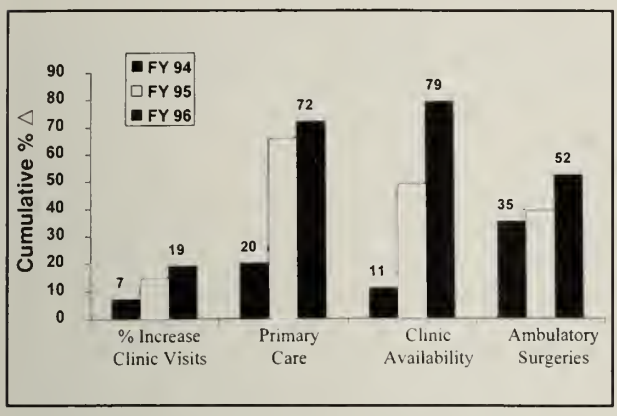

Figure 3.—Cumulative percent changes are shown in Veterans Affairs medical center clinic visits, clinic appointments available within 30 days, and ambulatory surgical procedures from 1994 to 1996.

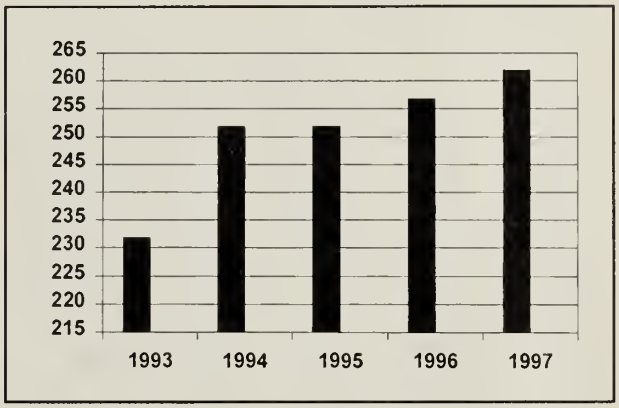

Figure 4.—The Veterans Affairs research appropriation

ble for eyeglasses or wheelchairs or to be admitted to a community nursing home.

The foregoing suggests that the VA may be able to survive in the competitive marketplace based on costs of care. How does the VA compare in terms of quality of care? The few comparative measures that are available suggest that the VA is in a competitive position. The 1996 Veterans Health Survey of more than 1,000 veterans compared health promotion and prevention services between veterans who received 90% or more of their care in the VA and those who received 90% or more of their care outside the VA.[7] Of the 13 measured indicators, the differences between VA and non-VA users were statistically significant for 6, and the VA users received better care in 5 of the 6—mammograms and counseling about tobacco, alcohol, nutrition, exercise, and seat-belt use. Some might question whether the Joint Commission for the Accreditation of Healthcare Organizations really assesses quality of health care. If this is assumed, then the VA has done remarkably well in this measure of health care quality by greatly improving the percentage of hospitals receiving commendation (no type I recommendations) from 0% in 1994 to 20% in 1996. Commendations are currently received by fewer than 10% of hospitals in the private sector. Veterans, the customers of the VA health care system, will ultimately determine whether or not the VA provides competitive services and quality of care as opportunities increase for aging veterans to receive care through Medicare health maintenance organizations.

The primary purpose in this presentation has been to describe the massive changes the VA is undergoing in its organization, with the goal of becoming a more efficient provider of higher quality health care to veterans. The foundation of a robust and competitive health care organization is crucial to the success of the other two missions the VA shares with its academic partners, medical education and research.

Medical Education and Research

A healthy system for medical education is characterized by constant questioning of the status quo, experimentation, and change. The VA has traditionally played a major role in our national medical education structure; more than half of all physicians receive some of their training in VA hospitals, and almost 10% of medical residency positions are funded by the VA. The good news in the education area is that the VA for the first time has identified the level of indirect support provided to medical centers for the costs of supporting medical education. This year the support is approximately $43,000 per medical residency position, and the total dollars added to academic VA medical center budgets to support education are as much as $5 million in the larger centers. Service chiefs need to know about this budget item as they negotiate for allocated teaching time for their physician staff.

Of greater concern are the proposed changes in residency support. In the past year the VA has recognized the national problem of oversupply of specialty physicians and has initiated a plan to contribute its share of the need to realign residency training programs. Last year a commission led by Robert Petersdorf, MD, responding to the recommendations of the American Association of Medical Colleges to realign residency training toward primary care, recommended that the VA reduce the total number of medical residencies by 3%, or 250 specialty positions.[8,9] This would take the VA back to the 1987 level of residency support. A similar move of non-VA–funded medical residencies back to the 1987 level would require a much larger 25% reduction, so in this context, the total reduction in residency positions by the VA does not appear to be large. Of particular concern is the much greater proposed reallocation of some 750 specialty residency positions to primary care positions over the next two years. This move is again in response to the recommendations of several national commissions that too many specialists are being trained and that the projected needs for primary care physicians are not being met. Although some scholars of health manpower

planning disagree with these proposals,[10] the common wisdom supports such a change, and some academic medical centers and medical schools are in the midst of similar reductions in their support for specialty training. The exact size of the reductions in support for specialty positions is still unclear. A residency oversight committee, chaired by Marvin Schleisenger, MD, has proposed that the reductions be primarily taken by programs that have the lowest workload and least quality, and it will be interesting to see how these features are measured and what their effect will be on the allocation. Consistent with the emphasis in the new VA organization on the VISN or network as the primary operational structure, the new residency allocations will be made to the VISNs, and final allocation to medical centers will have to be determined by committees with representatives from VAs and their affiliated medical schools. These upcoming negotiations between different VA medical centers and different medical schools at the VISN level, between VA medical centers and their affiliates, and between different specialty chiefs at the medical centers will test the ability of the various participants to cooperate.

In 1958 the US Congress formally recognized medical research as one of the three missions of the VA. Since then, each year it has formally authorized a portion of the VA's annual budget for research. With relatively modest funding ($262 million in 1996), the investment in VA research has been remarkably productive of discoveries that have improved the health of veterans. The VA has also supported a clinical scientist training program that has had excellent success in moving trainees into respected academic positions. With the recent congressional emphasis on balancing the federal budget has come an increasing concern for the health of the VA medical research budget. The VA research budget over the past five years has increased at an annual rate of 2.5% per year, a level of growth that lags behind the inflationary increases of the costs of conducting research (Figure 4). The net effect of this continuous underfunding of VA research has been to reduce the number of VA-funded medical research grants from 2,400 in 1988 to 1,600 in 1996. Further anxiety has been generated over the current administration's proposal to decrease the level of VA medical research to $234 million for the next fiscal year. When expected inflation is considered, the proposed reduction comes close to 15% compared with the current level of funding. Fortunately, support from the American Association of Medical Colleges, the Western Association of Physicians, the American Federation for Medical Research, and the Friends of the VA for an increased VA research budget of $280 million for next year appears to have led the veterans committees in both the House and the Senate to propose VA research funding levels for next year that should be slightly above those of 1997. There is still need for active support of a resurrected VA research budget as the revised proposal winds its way through the various authorization and budget committees to the president.

Threats to VA research support come not only from congressional and administration attempts to balance the budget, but also come from attempts at the VISN or hospital level to tap research resources, in particular the research time of clinical investigators, to support the unmet clinical needs of veterans and hospital budget deficiencies. Important good news in this regard is the identification of almost $500 million in the VA medical care budget for support of the research infrastructure. The VA medical centers' budget has always supported research by providing space, facility maintenance, and physician research time. For the first time, however, the level of this support has been identified as a separate part of the budget provided to each VISN director and to the individual facilities. The level of this support is considerable, approximating 75 cents for each dollar of VA, National Institutes of Health, and other directly funded research support. This amounts to more than $10 million added to the hospital budgets of several of the larger western VA medical centers. It is important that VA investigators know about this newly identified part of their hospital budget so that hospital and VISN managers will not be tempted to move these dollars to areas that do not support research.

Most of the recent changes in the VA research program have been in response to recommendations made by a high level Research Realignment Advisory Committee in 1996. In addition to the expected recommendations that the VA research budget be increased, this group recommended that the institutional costs borne by the VA in supporting National Institutes of Health and other extramural research be recovered from the indirect costs that are now often retained by affiliated universities. There has been considerable movement in this direction over the past two years, with some universities returning an appropriate amount of the overhead to the VA, and in other cases, nonprofit VA-affiliated research foundations have become the primary fund managers for the National Institutes of Health and other extramural agencies. Another recommendation of the Research Realignment Advisory Committee that has generated some anxiety was to accept the principle of designated research areas in organizing VA research. Designated research areas were defined as those areas of research that are of particular interest to veterans because of a high prevalence of conditions within the VA population (such as spinal cord injury or chronic obstructive pulmonary disease), or are of importance to the question of effective health care delivery within the VA. One rationale for this move was to be able to prove to Congress and other VA supporters that VA research was relevant to the needs of veterans. Experience after several rounds of funding in the past year indicates that the great majority of investigator-initiated proposals fell within the designated research areas, and apart from some shift in the balance of funding dollars from basic medical research toward health services research, the course of VA research will not veer far from the current emphases because those academicians who choose to

work in the VA are primarily interested in the clinical problems of their patients. This is the impetus for most high-quality clinical research.

Conclusions

The wrenching changes that are now occurring throughout health care are adding new stresses to the VA-academic affiliation. Funding sources are declining and shifting for both partners, and the changing priorities of patients and the marketplace are forcing physicians to consider new ways of practicing medicine and dealing with each other. The need to reassess the allocation of resident positions and the ways research overhead are handled are just two examples of areas where honest dialogue is needed. Despite these current stresses, the benefits of the affiliations have never been greater. The VA continues to be a relatively stable source of funding for clinical faculty. In many ways, the VA operates as a staff salary model health maintenance organization, and faculty income is not as dependent on monthly workload and income as are the clinical salaries in many medical schools where fee-for-service income predominates. In fact, in some affiliations, VA clinical faculty support exceeds that provided directly by the parent university. The VA is currently the nation's largest single provider of health professions education and training, and for several reasons, the VA is often the preferred training site for medical students and residents. Veterans are generally grateful patients who appreciate the value of having trainees participate in their care. Although the VA has in recent years appropriately expected increased supervision of residents and students, the documentation of this supervision has not been as onerous and counterproductive as that currently required by the Healthcare Financing Administration, and a challenging teaching environment is still possible in most VA medical centers.

The decision that was made more than 50 years ago to encourage VA medical centers to establish partnerships with medical schools was a wise one, and the rationale has not changed. Health care for veterans has improved by the recruitment and retention of the highest quality medical staff and by the establishment of a patient care environment that is characterized by an atmosphere of inquiry. Medical schools have gained a partner that provides a large clinical base for teaching and clinical research and a funding source for clinical faculty and research. It is difficult to identify a public-private partnership of this duration and magnitude that has been so mutually beneficial, and the opportunities for further mutual gains from this partnership have never been greater.

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Epitomes

Important Advances in Clinical Medicine

Otolaryngology

Terence M. Davidson, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in otolaryngology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in otolaryngology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Otolaryngology of the California Medical Association, and the summaries were prepared under the direction of Dr Davidson and the Panel.

Sleep Studies and Primary Care

OBSTRUCTIVE SLEEP APNEA is a common and serious medical illness affecting as many as 24% of adult men and 9% of adult women. Not only does obstructive sleep apnea leave the patient tired, unhappy, and nonproductive, but it is also associated with many of today's most serious illnesses, including obesity, hypertension, angina, myocardial infarction, transient ischemic attacks, stroke, congestive heart failure, end-stage renal disease, and diabetes.

Traditionally, sleep studies are performed by a small number of sleep medicine specialists using either in-hospital polysomnography or home sleep testing. The home sleep test is now so accurate and simple that it can be administered by a nurse or medical assistant under the direction of a physician. In Walla Walla, Washington, for example, local physicians were trained to conduct sleep studies and dispense nasal continuous positive airway pressure (nCPAP) machines; awareness of sleep apnea increased in the medical community as a result. Of 360 patients tested, 276 (76%) were diagnosed with obstructive sleep apnea, most of whom were successfully fitted with nCPAPs. The entire project was conducted by primary care personnel with the advice of the Stanford Sleep Medicine Program.

Sleep apnea is a prevalent and serious medical condition. An interested physician can successfully conduct home sleep studies, perform CPAP titrations, and prescribe nCPAP machines. As the medical community becomes aware of this disorder and the ability to diagnose it, more and more people will receive appropriate diagnosis and treatment.

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Vocal Cord Paralysis

INJURY TO ONE OR BOTH recurrent laryngeal nerves can have devastating effects on the basic laryngeal functions of respiration, phonation, airway protection, and swallowing. Bilateral vocal cord (vocal fold) paralysis frequently leads to airway obstruction and respiratory compromise, while unilateral vocal cord paralysis causes disturbances in voice production and swallowing, including aspiration. Typically, patients with combined superior and recurrent laryngeal nerve or high vagal nerve injuries have greater sensory and motor impairment of the hypopharynx and larynx, and thus more severe dysphagia and aspiration, than those with isolated recurrent laryngeal nerve injuries.

The most common causes of unilateral vocal cord paralysis are nonlaryngeal (mainly pulmonary) malignancies, surgical and iatrogenic trauma including prolonged intubation, and central and peripheral neurologic disorders. Idiopathic and virus-induced pareses often resolve before medical attention is sought.

Evaluation of patients with suspected unilateral vocal cord paresis includes a thorough history, complete head and neck, laryngeal, and neurological evaluations, chest radiography, and often computed tomography or magnetic resonance imagery (CT or MRI) of the skull base

through the thoracic inlet to rule out brainstem, neck, chest, and mediastinal sources. Blood tests and other specific studies are indicated if conditions such as diabetes mellitus, Lyme disease, or myasthenia gravis are suspected.

Laryngeal studies that can have both diagnostic and prognostic values include laryngeal videostroboscopy, laryngeal electromyography, and acoustic and aerodynamic measurements of laryngeal function. Swallowing function evaluation, including videofluoroscopic swallow studies with barium, are invaluable. Such tests document the degree of impaired function and evidence of reinnervation, to help predict prognosis for spontaneous recovery and influence degree and timing of intervention.

The primary treatment goals for the patient with unilateral vocal cord paralysis are to eliminate aspiration and improve voice. Enhancing the effectiveness of cough and Valsalva maneuvers is a secondary goal. If the cause of the paralysis is known and is irreversible (such as resection of the vagus nerve in conjunction with skull-base surgery), acute intervention is indicated. On the other hand, with an idiopathic paralysis, if voice, airway, and swallowing symptoms are not severe, it is reasonable to wait for six months to a year to allow for spontaneous recovery before performing any permanent correction procedure. The contralateral nonimpaired vocal cord may partly compensate for the paralyzed vocal cord in achieving glottic closure. Speech and language therapy helps the patient not only with voice quality but also with swallowing rehabilitation and with objective assessment of progress.

Surgical intervention is appropriate if spontaneous healing and voice therapy fail to achieve adequate recovery of laryngeal function. The principal surgical options include injection medialization, laryngeal framework surgery, and reinnervation procedures. All of them are directed at improving the position and bulk of the paralyzed vocal cord so that the still-mobile contralateral vocal cord can achieve glottic closure. Other procedures are used in cases of bilateral vocal cord paralysis with airway obstruction or intractable aspiration.

Injection medialization is probably the most common procedure performed worldwide, because of the ease of the procedure and the variety of materials that can be injected to bulk up and reposition the paralyzed vocal cord. Gelfoam (sterile cellulose sponge), collagen, and autologous fat are temporary to semipermanent substances, and Teflon comes as a nonabsorbable paste, that can be injected into the paralyzed vocal cord under local or general anesthesia. Teflon injection has disadvantages—it tends to become stiff and incite granuloma formation over time, and it is difficult to remove if vocal cord movement should return.

The most commonly performed laryngeal framework procedure is vocal cord medialization using an implant introduced via an external approach through the thyroid cartilage of the larynx. Silastic, cartilage, and hydroxylapatite implants have all been used successfully. The operation is performed under local anesthesia so that patient feedback and optimal voice results can be obtained.

Laryngeal reinnervation can be performed alone or in conjunction with the above procedures in an effort to preserve tone and bulk in the paralyzed vocal cord even in the absence of mobility.

Optimal management of the patient with unilateral vocal cord paralysis depends on an awareness of the potential causes, pathophysiology, consequences, and behavioral and surgical treatment options available. Primary care physicians must be familiar with the methods of diagnosing and managing vocal cord paralysis to make appropriate special care referrals to speech-language pathologists and otolaryngologists.

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Removing Double Chins—The Role of Submentoplasty

With aging there is often an increasing ptosis of the submental structures, resulting in loss of the normal upper neck concavity under the chin (sometimes called a "wattle"). This is due to an excess of submental fat plus laxity of the platysma muscles and loss of normal skin elasticity. The usual treatment is a rhytidectomy or facelift. Some individuals may not want a facelift for a variety of reasons, including cost. A much less involved procedure, submentoplasty, regularly produces sizeable improvement in the submental region and can be performed on outpatients under local anesthesia in a procedure room. Submentoplasty can be combined with a chin implant, since inadequate chin projection often contributes to the submental deformity. Liposuction of the adjacent lateral neck and jawline can be performed at the same time, if needed.

Submentoplasty consists of several steps. First, a small horizontal incision (3 cm) is made just under the chin. The incision may be carried down on one side in a boomerang shape over the anterior edge of one platysma to allow excision of excess skin in the left-right plane as well as the superior-inferior plane. A z-plasty excision can also be used. The incisions should remain above the level of the lower aspect of the hyoid bone so as to be inconspicuous. Excess fat in the subcutaneous area and fat deep to the platysma, between the anterior edges of this muscle, is then excised. The ptotic anterior edges of the platysma are sutured together and an appropriate amount of excess skin is removed, if necessary, after extensive undermining and skin redraping. Skin closure is performed without tension; a

drain is occasionally used. A supporting dressing is worn for two weeks after the surgery and then only at night for the first month. The submental scars heal well and are difficult to see, although patients should be warned that a scar will be present.

Patient satisfaction is high in patients whose primary deformity is in this area. The procedure can be combined with a conventional facelift to produce maximum improvement in the appearance of the neck.

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An Overview of Facial Wrinkles

FACIAL WRINKLES, or rhytids, are primarily a result of gravity and loss of elastic tissue support from collagen changes in the dermis. Their development is also hastened by ultraviolet light, lack of skin hydration, and tobacco smoke. With aging, the face also develops hyperdynamic facial lines, furrows caused by the repeated pull on the skin of underlying facial mimetic muscles, which are different from wrinkles (sagging skin). The pattern of hyperdynamic facial lines depends on whether the individual is an "eyebrow raiser," a "squinter," or a "frowner"—a pattern usually established by the age of 6 years.

Probably the most significant development in the treatment of facial wrinkles is laser skin resurfacing. Two types of lasers are used for skin peeling: pulsed CO_2 and erbium:YAG. They are well-suited for treatment of upper lip lines, periorbital dynamic lines (crow's feet), interbrow furrows (frown lines), sun damage, mild facial elastosis, shallow scars, and benign epidermal-upper dermal lesions. For many facial plastic surgeons, dermatologists, and plastic surgeons, laser skin resurfacing has all but replaced chemical peel and dermabrasion for these indications.

The pulsed CO_2 laser (wavelength of 10,600 nm) delivers pulses of laser energy of such short duration that there is minimal heat damage to surrounding skin. The energy is absorbed by the extracellular water in the target tissue. The pulses are also spaced in delivery to allow the tissue to cool between pulses. Each pulse removes 50–100 µm of tissue. In addition, the lasers are powerful enough to deliver high fluences (energy densities) so that excess heat is dissipated into the laser plume rather than into facial skin. The erbium:YAG laser has a wavelength of 2940 nm and causes true ablation of target skin. Each pulse removes only 25–30 µm of tissue.

The majority of patients who undergo laser skin resurfacing are satisfied with the results. The procedure is not a substitute for time-honored procedures such as facelift; the laser will not address deep facial folds (such as the nasolabial folds) and jowls. Infrequent complications are infection, scarring, hypopigmentation, and hyperpigmentation. While the pulsed CO_2 causes a "mini-facelift" effect by favorable collagen tightening, prolonged erythema accompanies its use. The erbium:YAG causes less erythema and more rapid healing. It therefore fills a distinct requirement for younger patients with fewer wrinkles.

A useful adjunct to the laser for the treatment of hyperdynamic facial lines is botulinum toxin A. Produced by the bacterium *Clostridium botulinum*, botulinum toxin A causes a flaccid paralysis of injected muscles by inhibition of release of vesicle-bound acetylcholine at the neuromuscular junction. The LD_{50} is estimated to be approximately 2730 IU in humans; doses on the order of 20–40 IU are used for cosmetic purposes. Although used clinically for many years for conditions such as blepharospasm and hemifacial spasm, it is frequently used for the treatment of crow's feet (orbicularis oculi muscle hyperactivity) and interbrow furrows (corrugator muscle hyperactivity).

The iatrogenic muscle paralysis induced by botulinum toxin A typically lasts for four to six months. The temporary nature of the procedure should be emphasized to patients. Possible complications are related to local muscle paralysis and include eyelid ptosis, eye irritation, double vision, and eyebrow drooping. Patients with known hypersensitivity to the toxin and those with Eaton Lambert syndrome should not receive botulinum toxin A treatment.

Patients also have direct access to over-the-counter products that can make small yet noticeable improvements in their skin quality. Products containing glycolic acid and topical vitamin C have been shown to improve skin elasticity and can be considered for superficial wrinkles.

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Alerts, Notices, and Case Reports

Severe Hypernatremia From Sea Water Ingestion During Near-Drowning in a Hurricane

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INGESTION OF SEAWATER, whether voluntary[1] or accidental,[2,3] and its clinical sequelae have not been amply reported in the literature. Although seawater ingestion has been directly observed in animal drowning experiments[4] and is believed to occur during human drowning,[2,3,5] it has not been reported to play a significant role in producing serum electrolyte abnormalities in near-drowning victims. Because of the high concentration of sodium in seawater (approximately 350 to 500 mmol per liter[10,11]), ingestion of this fluid and subsequent absorption of electrolytes can lead to hypernatremia. This condition is caused not only by the addition to the body of proportionately more sodium than water, but by water loss from solute diuresis or osmotic diarrhea.

The near-drowning patient whose case is reported in this paper experienced unusual circumstances as the result of a shipwreck during the height of a hurricane; the patient's immersion and involuntary seawater ingestion led to the development of severe hypernatremia. This case is interesting not only because of the patient's harrowing ordeal, but also because it illustrates the physiologic changes and clinical symptoms that can occur in a victim of near-drowning when significant quantities of seawater are ingested rather than aspirated. To my knowledge, the patient's serum sodium levels are the highest reported in the literature on near-drowning.

Report of a case

A 35-year-old fisherman was rescued by the United States Coast Guard on September 16, 1995, and flown to the emergency department at the US naval hospital in Puerto Rico. He had been found clinging to floating debris on the open sea following the passage of Hurricane Marilyn through the US Virgin Islands.[6] The patient had remained on board a fishing vessel that was moored in an unprotected harbor during the storm. On his recovery we learned that he had been forced to abandon his vessel at night after it broke from its anchorage, struck a reef, and was swamped by waves. He remained in the water (surface temperature 28°C [82.4°F]) for the next 11 hours (from about 9 PM on September 15 to about 8 AM September 16), during which time he was repeatedly submerged by breaking ocean swells (estimated to be more than 20 feet high). He also experienced sustained winds of 109 miles per hour, wind gusts up to 129 miles per hour, and the eye of the passing hurricane (written communication, Lieutenant Commander J.R. Jarvis USN, Officer in Charge, US Naval Atlantic Meteorology and Oceanography Detachment, Puerto Rico, December 1997). While submerged he involuntarily inhaled, "choked" on, and swallowed mouthfuls of water after reaching his breath-holding breaking point. Despite turbulent conditions, his life jacket kept him afloat during most of this episode.

The patient's medical, surgical, and family history were unremarkable, and he had not been taking medications. Immediately before his ordeal he was in good health, had not been deprived of water, and had no symptoms of thirst, polyuria, lassitude, or gastroenteritis. When the patient was specifically questioned after recovery, he recalled episodes of micturition while in the water.

On examination, the patient's rectal temperature 35.7°C (96.3°F); pulse rate while lying flat 120 beats per minute; blood pressure 90/50 mm of mercury; respiratory rate 30 breaths per minute; and weight 61 kg (136 lb). He was a thin man in moderate distress who spoke incoherently and was disoriented as to time and place. Examination of his head showed no evidence of trauma. His neck veins were flat, and his mucous membranes were dry. His gag reflex was normal. Fine crackles were auscultated at both lung bases. Cardiac examination revealed tachycardia without gallop or murmur. His neurologic examination revealed no focal deficits. Except for a few superficial abrasions on his right knee, the remainder of his physical exam was normal.

Values for serum chemistries and arterial blood gas samples that were collected before therapy are listed in Table 1 (Day 1). The patient's complete blood count revealed a hematocrit level of 40% and a leukocyte count of 24.4 (24,400 mm^3). His urinalysis revealed a pH of 5 and a specific gravity of 1.025. Urine electrolyte studies could not be performed. A serum screening for illicit drugs was negative. Thyroid function studies were normal. The results of the patient's blood cultures were normal. A chest radiograph revealed mild hypoinflation but was otherwise normal. An electrocardiogram showed sinus tachycardia with a heart rate of 120 beats per minute and left ventricular hypertrophy with repolarization changes.

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TABLE 1.—*Serum Electrolyte and Arterial Blood Analysis**

	Day 1						Day 2			Day 3
*Local Time**	*0918*	*0952*	*1330*	*1600*	*1800*	*2100*	*0520*	*0900*	*1800*	*1000*
*Time Hospitalized**	*00:00*	*00:34*	*03:38*	*06:42*	*08:42*	*11:42*	*20:02*	*23:42*	*32:42*	*44:42*
Weight (kg)	*61*						*62*			
*Labaratory test**										
Sodium (mmol/L)	175	174	164	159	154	147	142	142	143	142
Potassium (mmol/L)	5.1	5.0	4.3	3.9	4.1	3.9	3.4	3.4	4.6	4.3
Chloride (mmol/L)	148	147	138	132	128	119	115	115	114	112
HCO_3- (mmol/L)	15	15	12	12	12	14	19	19	21	24
Creatinine (mg/dl)	1.1	1.0	1.0	1.1	1.1	1.2	1.1	1.1	1.4	1.2
Urea nitrogen (mg/dl)	15	15	14	13	13	12	8	8	16	12
Glucose (mg/dl)	112									
Calcium (mg/dl)	8.3	8.8								
Phosphorus (mg/dl)	1.9	2.7								
Magnesium (mg/dl)	3.3	2.0								
Arterial Blaad Gas										
pH	7.19**		7.2**			7.3**		7.4**		
Partial pressure of CO_2 (mmHg)	45		32			29		34		
Partial pressure of O_2 (mmHg)	125		269			78		90		

*To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert values for glucose to millimoles per liter, multiply by 0.0SSS1. To convert values for calcium to millimoles per liter, multiply by 0.25. To convert values for phosphorus to millimoles per liter, multiply by 0.3229. To convert values for magnesium to millimoles per liter, multiply by 0.4114.

*Atlantic Standard Time.

*Time in hours and minutes from presentation to the emergency medicine department.

*Laboratory test data performed obtained using a Dimension XX AR clinical chemical analyzer. PN 715914.001; E. I. Du Pont de Nemours & Co., Inc., Wilmington, DE.

**Breathing 6L/min humidified oxygen by face mask.

**8reathing room air.

Initial therapy included high-flow supplemental oxygen administered through a face mask, application of warming blankets, and intravenous injection of a bolus of approximately 500 ml of isotonic saline. After the results of the patient's serum electrolyte levels became available, his intravenous fluids were changed to 5% dextrose in water. Because of concern that overly rapid correction of the patient's hypernatremia might lead to cerebral edema,[7] it was decided to correct the water deficit slowly over the next two days, while measuring serum electrolyte levels at frequent intervals and keeping the patient under close observation.

A water solution containing 5% dextrose was slowly infused. The patient's urine output during the first four hours of his hospitalization was 750 ml. Within 8 hours after presentation his sensorium cleared, he began to complain of severe thirst, and he experienced several episodes of diarrhea. Our attempts to limit his intake of water were unsuccessful. During brief periods when the patient was not under direct observation by the nursing staff, he was found voraciously drinking unknown quantities of water from a nearby sink. Total input volume of water for hospital day 1 could not be accurately measured. Total measured urine output was 2210 ml for hospital day 1. On the morning of hospital day 2 he was breathing normally, had normal mental activity, and was without complaint. His weight was 63 kg (140 lb), serum sodium concentration 142 mmol per liter (a decrease of 33 mmol per liter in 24 hours), and his leukocyte count had returned to normal. A repeated chest radiograph was unremarkable. His diet was increased and restrictions on oral water intake were relaxed. By the evening of hospital day 2, the only abnormal laboratory test parameter that persisted was mild hyperchloremia. On hospital day 3 he was discharged from the hospital, at which point he was able to walk and tolerate a full diet.

Two days following his discharge from the hospital, the patient traveled to mainland United States and remained there. Although further direct contact with the patient has not been made, acquaintances who have been in contact with him have stated that he has reported feeling well and has returned to work.

Discussion

Ingestion of hypertonic sodium solutions is a classic, uncommon cause of acute hypernatremia.[8] Even more unusual is the occurrence of severe hypernatremia in cases of water near-drowning at sea.[9] Despite the high

sodium concentration in ocean waters (approximately 350 to 500 mmol per liter[10,11]), the electrolyte values reported in retrospective series of patients suffering from drowning and near-drowning in this fluid have usually been in the normal range.[5,10–13] This is probably because submersion, and the subsequent chain of events—including struggle, aspiration, asphyxia, and hypoxemia (with closed or open glottis[3])—occur immediately and are interrupted in a matter of minutes by either rescue or death. Typically, there is neither time nor opportunity for electrolytes to accumulate in the extracellular fluid compartment (ECFC). The case of near-drowning reported here is unusual in that recurrent submersions resulted in ingestion and accumulation of the solute over a period of many hours.

When seawater is aspirated it causes impairment of alveolar gas exchange, which results in hypoxemia and chest abnormalities secondary to pulmonary edema and atelectasis.[5,7–14] The marked hypertonicity of the aspirate results in rapid fluid shifts: protein rich fluid from plasma moves into the lungs, and some solutes of seawater move into the plasma.[14] Although inhalation of salt spray whipped up by high winds was inevitable in this patient given the circumstances, the lack of radiograph findings coupled with his relatively mild degree of hypoxemia indicate that little seawater was actually aspirated—certainly not enough to have a significant effect on his volume status or serum electrolyte concentration.[10]

When seawater is swallowed, relatively poorly absorbed, osmotically active solutes such as magnesium, phosphates,[10] and particulate matter,[5] as well sodium and chloride, are added to the luminal content of the gastrointestinal tract. As a result, water translocates into the bowel, causing diarrhea, while sodium and chloride ions move along their concentration gradients from the lumen of the bowel to the ECFC. Seawater ingestion probably caused the diarrhea that occurred in this patient and also could have contributed to his hypovolemia.

Another factor contributing to the patient's hypernatremia and hypovolemia was polyuria. The high urine output observed during the initial hours of his hospitalization revealed that diuresis was occurring despite the apparent presence of hypovolemia. The polyuria was likely secondary to the combined physiologic effects of head-out water immersion,[15] mild hypothermia,[16] and solute diuresis induced by the ingestion of hypertonic seawater.[17,18] Because the sum of the concentrations of sodium plus potassium in seawater ($SW_{[Na]} + SW_{[K]}$) is higher than the sum of the concentrations of these electrolytes in human urine ($U_{[Na]} + U_{[K]}$), ingestion of seawater results in the addition to the body of more sodium plus potassium than water, or a positive tonicity balance.[18] In this setting, production of urine that is relatively more diluted than ingested fluid causes simultaneous accumulation of solute and loss of free water to and from the ECFC. Moreover, if urine volume plus stool water volume are greater than the volume of seawater ingested, the total amount of water in the body will decrease. This process results in a self-perpetuating cycle of sodium gain and water loss that continues until interrupted by the cessation of seawater ingestion and/or the administration of appropriate volumes of free water.[18]

The patient's severe electrolyte imbalance and clinical presentation resulted primarily from seawater ingestion and consequent water loss from the gastrointestinal tract and kidneys, rather than from the aspiration syndrome typically seen in cases of near-drowning. I base this conclusion on the patient's normal chest radiograph and lack of pulmonary complaints,[10–14] as well as on previous reports of seawater ingestion, which also involve polyuria despite hypovolemia[17,18]; postresuscitation diarrhea[1]; hypernatremia[3,9]; hypermagnesemia[2,14]; and persistence of hyperchloremia after free water replacement.[1,5,9,14] Although higher serum sodium values have been observed in dehydrated Cuban refugee rafters who voluntarily drank seawater (personal communication, K. Candiotti MD, Jackson Memorial Hospital, Miami, Florida, March 1997), I believe the patient presented in this paper had the highest serum sodium level reported in the literature after involuntary ingestion of seawater during an episode of near-drowning. In the three days following his severe hypernatremia he did not appear to be adversely affected by the precipitous decrease in his serum sodium level, although the rate of change far exceeded the threshold above which patients are considered to be at risk for cerebral edema.[7] A longer follow-up period might be required to definitively prove a lack of significant central nervous system sequelae in this patient. Unfortunately, a longer follow-up period was not possible in this case, although reports from the patient's acquaintances indicate he is doing quite well and has returned to the activities of daily living.

The case reported here demonstrates that severe symptomatic hypernatremia can occur as a result of near-drowning episodes when significant amounts of seawater are swallowed rather than aspirated. The effects of seawater ingestion may be important components of the abnormalities observed in near-drowning victims who experience recurrent involuntary submersion in rough seas. Accordingly, controlled administration of free water, whether orally or intravenously, should be a part of the patient's resuscitative regimen.

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Long-Term Remission of HIV-Associated Thrombocytopenia Parallels Ongoing Suppression of Viral Replication

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THROMBOCYTOPENIA MAY be found at any stage of human immunodeficiency virus (HIV) infection.[1] Its prevalence increases as HIV disease advances, with ranges reported of 20% to 45% from the early to the late stages of infection.[2] The mechanisms producing HIV-associated thrombocytopenia are likely multifactorial, with evidence for both decreased platelet production and increased immune system destruction.[3–9] Pharmacotherapy against HIV may result in thrombocytopenia,[2,10] although zidovudine, the most-studied antiretroviral agent in this clinical setting, is more likely to cause leukopenia and anemia.[11]

Treatment options for symptomatic or life-threatening HIV-associated thrombocytopenia have relied on the use of zidovudine alone or in combination with prednisone followed by splenectomy for refractory cases.[2,12–14] Corticosteroids produce a response in most HIV-infected persons but, after tapering, fail to induce a lasting remission. In addition, concerns exist over their potential for further immunosuppression.[2] Intravenous immune globulin therapy is variably effective because of its rapid onset of action but short-lived benefits.[2,15] The use of interferon alfa 2b may improve platelet counts, but it requires indefinite therapy at high costs and has poor patient acceptability.[2,16] One study found a short course of high-dose dexamethasone able to induce a remission in a small number of patients.[17]

The literature on antiretroviral therapy for HIV-associated thrombocytopenia has been limited to the use of zidovudine monotherapy. This use has been hampered by a previous inability to document its efficacy against HIV, relying on insensitive surrogate markers such as p24 antigenemia.[2,7,18–20] Therapeutics against HIV infection have evolved to a more aggressive approach that uses combinations of antiretrovirals while monitoring viral load to assess the treatment response.[21–27] We report the successful management of a case of HIV-associated thrombocytopenia in which long-term remission was maintained with dual nucleoside analog therapy alone in association with the ongoing suppression of viral replication.

(Zell SC, Peterson K: Long-term remission of HIV-associated thrombocytopenia parallels ongoing suppression of viral replication. West J Med 1997; 167:433–435)

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Report of a Case

The patient, a 42-year-old homosexual man, was seen at an urgent care facility because of epistaxis and ease of bruising over a three- to four-week period. A complete cell count was done and found to be normal except for a low platelet count of 15.0×10^9 per liter (15,000 per mm^3). Hospital admission was immediately arranged under the care of a hematologist.

The patient's medical history was remarkable only for a previous bout of viral hepatitis, type unknown, and occasional bouts of allergic rhinitis. Basically healthy, he used antihistamines for sinus relief and ibuprofen on occasion for pain and only drank socially. The patient engaged in risky sexual activity and reported a negative HIV test taken four years ago.

A physical examination revealed normal vital signs. Pertinent findings were limited to the skin, which showed multiple petechiae and large ecchymotic lesions on both lower legs and the right forearm. No manifestations of HIV infection or related opportunistic infections were noted.

The patient was given intravenous immune globulin (IVIG), 800 mg per kg over 12 hours on two consecutive days for presumptive treatment of immune thrombocytopenic purpura (ITP). Per his request, an enzyme-linked immunosorbent assay test to screen for HIV infection was obtained with a positive result confirmed by Western blot analysis. A CD4 lymphocyte count revealed 364×10^9 per liter (364,000 cells per mm^3). The patient was released on the fourth day with a platelet count of 91×10^9 per liter.

In follow-up two weeks later, the patient's platelet count had fallen to 12×10^9 per liter. He again received IVIG, a single dose of 400 mg per kg, as an outpatient

TABLE 1.—*Platelet Count and Viral Load Response to Therapy*

	Week of therapy													
Variable	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*15*	*19*	*23*	*27*	*35*	*43*	*51*
Platelet count, $\times 10^9$/liter	10	81	108	—	139	—	94	81	72	78	89	110	116	—
Prednisone dose, mg	60	60	40	40	20	10	5	0	0	0	0	0	0	0
Antiretroviral therapy, mg	(a)	→	(b)	→	→	→	→	→	→	→	→	→	→	→
Viral load, copies/ml	12,320	—	—	—	—	—	<130*	<400†	<400†	—	—	<400†	—	<400†

AZT = zidovudine, ddC = zalcitabine, → = same antiretroviral pharmacotherapy as the week before, — = the particular laboratory value was not obtained that week.

(a) AZT, 200 q8hr (every 8 hours), ddC 0.375 q8hr.
(b) AZT 200 q8hr, ddC 0.75 q8hr.
*Labcorp of Burlington, North Carolina, reported 130 copies/ml as their lowest limit of detection.
†Specialty Laboratories of Santa Monica, California, reported 400 copies/ml as their lowest limit of detection.

but failed to have an increase in the platelet count. A referral was made to an internist experienced in HIV patient care.

A decision was made to initiate combination antiretroviral therapy with oral zidovudine, 200 mg, and zalcitabine (dideoxycytidine), 0.375 mg, every 8 hours. A baseline measurement of the viral load done by polymerase chain reaction (Amplicor PCR RNA by Roche Laboratories, Burlington, NC) revealed 12,320 copies per ml. Prednisone also was prescribed, 60 mg daily, but tapered quickly over a six-week period because of weight gain and the development of a subcapsular cataract.

Table 1 chronicles the patient's platelet count, drug therapies, and subsequent viral load measurements. By week 1, the platelet count rebounded to 81×10^9 per liter. At week 6, a posttreatment HIV-1 RNA level was below the assay detection limit and continued to remain so throughout the 12-month follow-up period. Platelet counts continue to remain in a target range (72 to 116×10^9 per liter) without a need for oral prednisone therapy. The patient remains asymptomatic and does not have complaints or opportunistic infections associated with HIV infection.

Discussion

Although the mechanisms producing HIV-associated thrombocytopenia are likely multifactorial,[3–9] there has been a tendency toward therapy directed at reducing immune-mediated platelet destruction through the use of oral corticosteroids. Efforts at inhibiting viral replication using nucleoside analogs, predominantly monotherapy with zidovudine,[2,12–14,18–20] develop from the belief that antiretroviral therapy may reduce viral replication, driving cross-reacting antibody production and leading to platelet sequestration.[2,4,7,9] Other postulates of zidovudine's efficacy in this disorder have been attributed to its ability to concentrate in the bone marrow, thereby attenuating the adverse effects of HIV infection on megakaryocyte production of platelets.[2,4,6,8] In light of zidovudine's modest effect on inhibiting viral replication, however, ascribing prior treatment successes for HIV-associated thrombocytopenia to effective viral suppression is difficult without viral load measurements.

After unsuccessful IVIG therapy, our patient had a brisk and impressive rebound in platelet count with the use of both oral prednisone and a combined regimen of antiretroviral agents. The initial rebound in the platelet count cannot be attributed solely to the use of antiretroviral drugs; By week 6, however, oral prednisone had been discontinued because of adverse effects, but the patient's HIV-1 RNA level fell below the detection limit, demonstrating the efficacy of his antiretroviral regimen. The maintenance of platelets in a well-accepted range continues with the use of combined nucleoside analogs alone and the ongoing documentation of viral replication suppression. Because more than 75% of persons receiving prednisone typically relapse following its discontinuation,[2] our unexpected long-term remission of 52 weeks is gratifying and may imply an association between effective HIV suppression and diminution in associated thrombocytopenia.

In this era of new knowledge regarding the kinetics of HIV replication, early-stage thrombocytopenia may primarily be a manifestation of the active driving force behind this disease—viral replication. Because our patient did not consent to undergo bone marrow aspirations before and after treatment, we cannot exclude the possibility of an improvement due to increased megakaryocyte production. It may be of interest to study combination drug regimens that avoid the use of agents that concentrate in the bone marrow. If reports of increased platelet survival were to parallel the documentation of viral suppression, such data might support the hypothesis that thrombocytopenia is an immune-mediated phenomenon driven by HIV viral replication. In light of the adverse effects of oral corticosteroids, HIV practitioners may wish to consider a potent regimen of antiretroviral agents that includes dual nucleoside analogs

plus a protease inhibitor as initial therapy for early thrombocytopenia in symptomatic, non–life-threatening circumstances, with close monitoring of viral load measurements to assess efficacy.

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Reversible Muscle Weakness in Patients With Vitamin D Deficiency

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FOCAL AND DIFFUSE musculoskeletal symptoms are common in patients with metabolic bone disorders.[1,2] In patients with cases of vitamin D deficiency (hypovitaminosis D), the associated muscle weakness has a proximal distribution and variable severity.[2,3] In children with rickets and in adults with established osteomalacia, the muscle weakness can be quite debilitating.[4,5] Homebound older persons are at increased risk for vitamin D deficiency,[6] and the infirmity of old age may conceivably be due, at least in part, to such metabolic factors.[7] In contrast, vitamin D deficiency is rarely an obvious etiologic factor when relatively young and active adults have prominent muscle weakness.

Elaborate diagnostic workup to exclude other causes of myopathy may be appropriate but should not be allowed to interfere with the timely correction of vitamin D deficiency. Our experience and studies from the literature are consistent with a good prognosis for myopathic hypovitaminosis D, although recovery following repletion of vitamin D is slow and variable.

We report on two patients who presented with significant proximal muscle weakness, one with vitamin D malabsorption and one with dietary vitamin D deficiency. A search for inflammation or other causes of myopathy was negative. Muscle biopsy in one patient revealed type IIB fiber atrophy. Once normal serum 25-hydroxyvitamin D_3 levels were restored, both patients experienced gradual muscle strength improvement and reversal of proximal myopathy within 6 months.

Report of Cases

Patient 1

The patient, a 57-year-old woman, was seen in the Endocrinology Clinic at Washington University Medical Center (St Louis, Missouri) for the evaluation of musculoskeletal pain and weakness. About six months before the referral, the patient started to experience left lower

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rib and back pain, which was initially attributed to muscle injury sustained during swimming. She had tried over-the-counter pain medications without relief. The patient also had noticed muscle aches, progressive lower extremity muscle weakness, and difficulty in climbing stairs and getting up from a sitting position. She had always been an active person but had curtailed her physical activity because of easy fatigability. Despite a normal diet, she had lost about 13.6 kg (30 lb) in the preceding six to nine months. Her stools had become bulky, greasy, and malodorous. In the past year, she had sustained bruises more easily. She had no hair loss, cold or heat intolerance, melena, hematochezia, nausea, or vomiting. The patient's history included depression and iron deficiency anemia. There was a family history of diabetes mellitus, hypertension, and cardiovascular disease.

On physical examination, the patient appeared healthy and well nourished. Her weight was 74 kg (163 lb), pulse rate 68 beats per minute, blood pressure 134/86 mm of mercury, and temperature 36.5°C (97.7°F). Cardiac examination revealed a soft 2/6 systolic murmur. On neurologic examination, the patient was unable to rise from the squatting position without assistance. Lying supine, she was unable to raise her lower limbs against mild resistance. There was no muscle atrophy or tenderness, and deep tendon reflexes were normoactive. Sensation was intact, and her gait was unremarkable.

Complete blood counts and serum values for hemoglobin, electrolytes, creatinine, and urea were within normal limits. Serum 25-hydroxyvitamin D_3 was undetectable, serum total and ionized calcium levels were subnormal, and the serum intact parathyroid hormone (intact PTH) level was elevated (Table 1). Radiographs of the axial and appendicular skeleton were unremarkable. A urinalysis was normal. A fecal fat analysis showed steatorrhea: 91.9 grams of fat per 24 hours, corresponding to 54% of total fecal solids (normal, <20%). The serum level of vitamin E was remarkably low at 14 µmol per liter (0.6 mg per dl) (normal, 106 to 395 µmol per liter [4.6 to 17.0 mg per dl]), but the levels of vitamins A and B_{12}—514 µg per and 220 pmol per liter (299 pg per ml), respectively—were within normal ranges. The prothrombin time was slightly prolonged. A fasting lipid profile showed normal LDL cholesterol and triglycerides levels, and an HDL cholesterol level of 19 mg per dl (normal, 35 to 999 mg per dl). The results of thyroid function tests were consistent with subclinical hypothyroidism, or euthyroid sick syndrome (Table 1). Results of a biopsy of the small intestine showed marked blunting—shortening and flattening of the duodenal villi—consistent with nontropical sprue (celiac disease).

Based on the clinical presentation and laboratory test results, a diagnosis of vitamin D deficiency due to malabsorption was made. The patient was started on oral vitamin D therapy, 50,000 units of ergocalciferol per day. A gluten-free diet was instituted. On this regimen, the steatorrhea abated, the patient began to gain weight, and the serum 25-hydroxyvitamin D_3 level returned to normal within two months. Her muscle strength improved steadily during follow-up examinations and had returned to normal within six months.

Patient 2

A 19-year-old man was admitted to Barnes Hospital at Washington University Medical Center for the evaluation of progressive lethargy, fatigue, and muscle weakness. A resident of Nepal, the patient had traveled to the United States for medical treatment. For two years he had had progressive leg weakness associated with difficulty in climbing stairs and standing up from a sitting position. He also had proximal upper extremity weakness, which was somewhat less severe than the weakness he had been experiencing in his legs. He said that his walking pace had become slower, and that he had burning pains in both feet upon prolonged walking. The patient had been a strict vegetarian all his life, eschewing all animal products, including eggs and dairy products. He worked long hours in an office, with little exposure to sunlight. He had no history of diarrhea, nausea, vomiting, hair loss, dizziness, or blurred vision. He did not use alcohol, tobacco, or illicit drugs.

On physical examination, the patient was a fully developed, obese young man. His weight was 106.6 kg (235 lb), pulse 79 beats per minute, blood pressure 130/74 mm of mercury, and temperature 36.8°C (98.2°F). The patient had a broad-based "waddling" gait. He was unable to rise from a squatting position or get out of a chair without assistance. Lying supine, his proximal muscle strength was easily overcome by mild resistance in the lower extremities and by moderate resistance in the upper extremities. There was no atrophy or tenderness in any upper or lower extremity muscle groups. Deep tendon reflexes were normoactive, with flexor plantar responses; light touch, pinprick, joint position, and vibration sensory modalities were intact. The findings of the remainder of the physical examination were unremarkable.

Complete blood counts and serum values of hemoglobin, uric acid, electrolytes, creatinine, and urea were within normal limits. The serum creatinine kinase level was 394 units per liter (normal, 26 to 190 units per liter), and the sedimentation rate was 28 mm per hour (normal, 2 to 10 mm per hour). Serum total and ionized calcium levels were low, a 25-hydroxyvitamin D_3 level was undetectable and intact PTH and 1,25-dihydroxyvitamin D_3 levels were elevated (Table 1). The patient's two-hour postprandial plasma glucose level was 7.4 mmol per liter (134 mg per dl), with a hemoglobin A_{1c} level of 5.8% (normal, 4.1% to 6.3%). Serum alkaline phosphatase and hepatic aminotransferase levels were elevated (Table 1), but results of a screening for hepatitis B and C were negative, as were serologic tests for anti–smooth muscle, antimitochondrial, and antinuclear antibodies. His vitamin E serum level was 225 µmol per liter (9.7 mg per dl); vitamin B_{12}, 110 pmol per liter (150 pg per ml); and folic acid 8 pg per ml (normal, 5 to 20 pg per ml). A urinalysis showed no glycosuria or proteinuria; the 24-hour-urine free cortisol level was 77 µg

TABLE 1.—*Blood Chemistry Values in Patients With Muscle Weakness*

Chemistry Values	*Patient 1*	*Patient 2*	*Normal range*
Total protein, grams/dl	6.2	8.4	6.0–8.5
Albumin, grams/dl	3.8	4.7	3.2–5.0
Calcium, mg/dl			
Total	7.9	8.3	8.5–10.3
Ionized	4.5	3.3	4.6–5.3
Phosphorus, mg/dl	3.1	2.3	2.5–4.5
Alanine transferase, U/liter	50	198	0–48
Aspartate transferase, U/liter	43	167	0–48
Lactate dehydrogenase, U/liter	188	304	80–230
Alkaline phosphatase, U/liter	248	527	20–125
25-hydroxyvitamin D_3, ng/ml	<5	<5	10–55
1,25 dihydroxyvitamin D_3, pg/ml	N/A	140	15–60
Total cholesterol, mg/dl	74	256	<200
Intact Parathyroid hormone, pg/ml	518	227	11–54
Thyrotropin, U/ml	19.4	5.4	0.6–6.5
Thyroxine, µg/dl	5.6	12.5	4.5–12
Free thyroxine index	1.88	3.4	1.5–4.5

* To convert the values of calcium to millimoles per liter multiply by 0.250. To convert the values of phosphorus to millimoles per liter, multiply by 0.3229. To convert the value of cholesterol to millimoles per liter, multiply by 0.02586. To convert the values of 25-hydroxyvitamin D_3 to nanomoles per liter, multiply by 2.496. To convert the values of 1,25-dihydroxyvitamin D_3 values to picomoles per liter, multiply by 2.400. To convert the values of thyroxine to nanomoles per liter, multiply by 12.87.

per day (normal, 20 to 90 µg per day). A liver biopsy showed evidence of mild steatonecrosis. Radiographs showed bilateral diffuse demineralization of the distal radius, ulna, and metacarpals with slight widening of their physeal plates (Figure 1). There was no evidence of Looser's zones or pseudofractures in the skeleton. A biopsy of the left deltoid muscle, done after a neuromuscular consultation, revealed mild atrophy of type IIB fibers, without evidence of inflammatory disease.

A working diagnosis of myopathy due to severe dietary vitamin D deficiency was made. Associated mild vitamin B_{12} deficiency also was diagnosed. Treatment with oral vitamin D began at an initial dosage of 50,000 units of ergocalciferol per day, and the patient was discharged on 50,000 units twice a week. He also received dietary calcium supplementation (3 grams per day), and two vitamin B_{12} injections while in the hospital, followed by daily oral multivitamin supplements after discharge. His serum calcium and vitamin D levels returned to normal within a month. The patient's muscle strength improved gradually; he was able to rise from the squatting position with steadily increasing speed from about the second month of treatment. Follow-up examination after four months of vitamin D therapy indicated minimal residual proximal muscle weakness, which did not interfere with his daily activities. He has since returned to Nepal and remains fully active on vitamin D supplementation.

Discussion

Prospective studies have suggested that the incidence of proximal muscle weakness in patients with established osteomalacia may be as high as 73%[5] to 97%.[8] In studies from the late sixties and early seventies, osteomalacia was diagnosed on the basis of biochemical aberrations (hypocalcemia, hypophosphatemia, increased alkaline phosphatase levels), radiological evidence (Looser's zones), and bone biopsy specimens(the presence of excessive osteoid tissue).[5,8] Precision assays for vitamin D metabolites and intact PTH in serum were not routinely available at the time of those studies.

The mechanism of the frequent, and sometimes disabling, muscular weakness that complicates severe vitamin D deficiency is not fully understood. Putative pathophysiologic factors include an ill-defined myopathic process, evident on electromyographic studies but not histologically characterized[5]; a neuropathic process associated with secondary hyperparathyroidism[4]; a combined neuro-myopathy syndrome[8]; and a possible defect in vitamin D–mediated calcium transport into myocyte sarcoplasmic reticulum.[10] Notably, both of our patients had readily demonstrable proximal muscle weakness but normal findings on neurologic examination. Although patient 2 gave a history of a burning sensation in the feet and was found to have a slightly reduced serum vitamin B_{12} level, the severe muscle weakness cannot be attributed to a recognized vitamin B_{12}–associated mechanism. Similarly, although some myopathic syndromes (Hoffman's Syndrome in adults and Kocher-Debré-Sémélaigne syndrome in children) are associated with severe hypothyroidism,[11] subclinical hypothyroidism in patient 1 is an unlikely explanation for her prominent muscle weakness. Thus, a neuropathic mechanism was not clinically evident in our patients, despite the presence of secondary hyperparathyroidism, which has been suggested to induce muscular weakness through a neuropathic process.[4]

Figure 1.—A radiograph of the left wrist of patient 2 shows diffuse demineralization of the distal radius, ulna, and metacarpals, with slight widening of physeal plates.

In contrast, the muscle enzyme creatinine kinase level was elevated in patient 2, a finding that has been reported in a minority of patients with vitamin D–related muscle weakness.[3,12] Further, this patient's muscle biopsy specimen showed type IIB fiber atrophy, which also has been reported in previous studies.[3,4] In general, however, the results of electromyography and muscle biopsy tend to be nonspecific.[4,5,7,13]

Because vitamin D deficiency is a major cause of osteomalacia, the current diagnostic approach emphasizes the measurement of 25-hydroxyvitamin D_3 levels together with relevant biochemical indices. X-ray film studies are useful for documenting pseudofractures and other deformities; bone biopsy, however, is no longer required for the routine diagnosis of osteomalacia. The serum level of 1,25-dihydroxyvitamin D_3 tends to be normal or higher than normal as a result of the compensatory induction of 1 α-hydroxylase by the increased serum PTH levels. The incidence of muscle weakness in patients with vitamin D deficiency without the skeletal hallmarks of osteomalacia or rickets is unknown, but it may well be substantial. The presence of osteomalacia apparently is not necessary for the development of muscle weakness in persons with vitamin D deficiency.[9]

Regardless of the precise underlying mechanism(s), the recognition of vitamin D deficiency as a cause of reversible debilitating muscle weakness is important for clinical decision making. In a patient with proximal muscle weakness of any severity, finding a typical constellation of biochemical alterations (hypocalcemia, hypophosphatemia, elevated alkaline phosphatase, and a subnormal 25-hydroxyvitamin D_3 level) should limit the scope of further expensive and invasive neuromuscular workup for other causes of muscle dysfunction. In such a patient, an early therapeutic trial of vitamin D is warranted. After the serum levels of 25-hydroxyvitamin D_3, calcium, phosphorus, alkaline phosphatase, and intact PTH have returned to normal, the patient's muscle strength should be evaluated objectively for evidence of recovery.

The ultimate proof of the diagnosis of vitamin D–deficient muscle weakness rests on the response to therapy. Improvement in muscle strength has been observed as early as after a week,[5] but usually within one to two months,[14,15] of treatment with pharmacologic doses of vitamin D. Treatment is required for several months, however, for complete recovery of muscle strength.[13,15] Some authors have reported a pattern of incomplete recovery, as evidenced by persistent deficit in maximum voluntary isometric quadriceps strength during follow-up on long-term vitamin D therapy.[9] We have found the "squat-stand" timing test to be a useful semiquantitative bedside method of observing proximal muscle strength. Initially, weak patients are unable to stand from the squatting position and are assigned the worst baseline "squat-stand" time of infinity. Following appropriate treatment, patients are able to rise (albeit slowly) from a squatting position. The time needed to reach a fully upright posture, which can be recorded as part of the follow-up office notes, is inversely related to the proximal muscle strength. A lack of objective improvement in proximal muscle strength (documented by "squat-stand" times) after about a month on an adequate dosage of vitamin D indicates a need for reevaluation of the diagnosis.

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Editorial

Respiratory Therapist-Driven Protocols

ARE RESPIRATORY THERAPIST–DRIVEN protocols safe? Do they permit more timely and appropriate interventions in patients? Does this translate into better patient outcome? Do protocols save money and are these savings real or trivial? Many hospitals have adopted guidelines for a variety of respiratory therapy services. In this issue of THE WESTERN JOURNAL OF MEDICINE (see page 408), James K. Stoller, MD, proposes that respiratory therapy-driven protocols, as compared with traditional physician-driven practices, better apportion hospital resources and save money. While many hospitals have employed situation specific algorithms (e.g., weaning guidelines for the post-operative patient), Stoller, in previous work[1] has also advocated a respiratory therapy consult service.[1] In such a model, a physician requests consultation from a therapist evaluator (a senior respiratory therapist) who, after assessing the patient, chooses the most appropriate interventions (with accompanying algorithms) from the modalities available. From his study description, these therapists underwent extensive training that included lectures, review of algorithm care plans at each shift, and graded case studies every few months. Stoller found that use of a respiratory care consult service, as compared with physician ordered interventions, had a higher rate of "appropriate" respiratory orders. "Appropriate" was defined as in concurrence with algorithms from clinical practice guidelines of the American Association for Respiratory Care. Of note, chart review found that 15% of the initial orders written by this respiratory care consult service did not follow these same practice guidelines, despite the training listed above. Although this 15% was better than the 43% of physician orders for respiratory care that were discordant with clinical practice guidelines, this does raise some concerns for safety. In addition, would this low rate of "discordant" orders by therapists deteriorate over time? Would part-time and registry respiratory therapists be able to make similar quality assessments and plans for patients? Could this model be used successfully in other institutions? None of these answers is known.

See Commentary, pages 408–410

In the article in this month's journal,[2] Stoller reviews several articles that address the use and misuse of respiratory therapy resources. He found that over-ordering was more common than under-ordering in the studies that looked at both sides of resource allocation. Of note, five of the seven articles listed in Table 1 only addressed over-ordering. This bias may lead some institutions to think that that adoption of protocols may lead to substantial cost savings. It may not, if recognizing and correcting underutilization of resources is also a goal of protocols, as it should be. In Stoller's review, over prescription of supplemental oxygen was the most common misallocation. Is this important? Many physicians might argue that low flow oxygen is innocuous and provides a safety buffer despite adequate measurements of oxygenation at single points in time. Others may counter that while the cost to a single patient of low flow oxygen may seem trivial, the cumulative costs for a hospital over the course of a year could be substantial. Per Stoller's calculations, the potential savings with better allocation of supplemental oxygen for one year at his institution could be over $250,000. Even if the actual savings were a quarter of this estimate, the dollars saved could potentially be used for an additional respiratory therapist. Other examples of over-ordering in this review include inappropriately requested Arterial Blood Gases and Intermittent Positive Pressure Breathing treatments. Two of the six studies found misallocation of bronchodilator therapy.[3,4] Aerosolized bronchodilator therapy is commonly prescribed to in-patients despite the equivalent efficacy of bronchodilators by metered dose inhalers (MDIs) (if equivalent dosages of medication are given). Estimates that suggest that MDI use is significantly cheaper than nebulized therapy for hospitalized patients may not have had realistic labor costs for MDI use.[5] For an institution, a substitution protocol of MDI use for nebulized therapy may only be substantially cheaper if a significant portion of patients can self-administer their medication.

Beyond the issue of misallocation of resources, Stoller also cites articles that support improvement in specific scenarios by protocols such as earlier extubation of post surgical patients. We have had the same experience in our ICU; protocols have permitted earlier extubation and shorter ICU length of stay for our post coronary bypass patients without an increased rate of re-intubation or other adverse events.

In summary, this review by Stoller presents an increasing body of literature supporting the use of respiratory therapy driven protocols. Are they safe? There is evidence that respiratory therapy driven protocols follow expert opinion more closely than physician driven orders, at least in those institutions with expertise. This not quite the same issue as safety, and I would like to see more articles rate the "value" of misallocation of resources. To give the same example as above, prescribing low flow oxygen despite adequate oxygen saturation is unlikely to have the same medical consequences as not prescribing oxygen in a patient with hypoxemia. Do respiratory therapy driven protocols permit more timely and appropriate interventions in patients? I believe they do in specific pre-determined scenarios, such as earlier

extubation of post-surgical patients. Stoller also supports the concept of an evaluation and treatment respiratory consult service, with a broader scope of decision making. Regardless of the scope of care, the best protocols are developed as a collaborative process with input by therapists and physicians whose patients would be treated. Protocols developed solely by respiratory therapy departments without consulting the end-users may be poorly accepted by physicians. Do respiratory therapy driven protocols translate into better patient outcome? According to Stoller's previous work,[1] patients at least do not appear to have a worse outcome. Protocols that permit earlier extubation may translate into lower rates of nosocomial infection, but this remains to be demonstrated. Lastly, do respiratory therapy driven protocols save money and are these savings real or trivial? In Stoller's previous work,[1] the use of a respiratory care consult service did not decrease the cost of respiratory services, though he cites other examples of possible savings. Other estimates of potential cost savings have been extrapolated from short observational periods; it is unclear if significant savings can be realized. However, cost savings should be only one goal of such protocols. The primary goal should be better patient care.

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Special Series—Introduction

A Few Words About *The Quest for Mercy*

Roger Bulger, MD, FACP, is a man with a good memory and a great heart. Last year, we wrote several colleagues to announce that The Western Journal of Medicine had weathered its time of troubles and to request that they keep the journal in mind when they wrote papers of exceptional merit. Dr. Bulger remembered that letter as he prepared the manuscript of a book on mercy and managed care. Reviewers urged him to seek wide distribution of the finished piece, perhaps via the lay press. He thought the journal would be a better venue since his work is aimed at physicians and other clinicians, including young physicians and medical students. His goal is to engage more than those in medicine, however. He also hopes to touch patients, families, policymakers, and indeed the public as a whole.

Dr. Bulger's book addresses managed care and managed cost, of course. It also addresses sickness and healing, hope and despair, relationships, oaths, populations, prevention, and patients. In an afterward, Dr. Bulger discusses the tensions between idealism and reality, between our profession and our lives.

Dr. Bulger writes with authority and passion. He trained in medicine at the University of Washington and Harvard, was medical director of the University of Washington Hospital, and then served on the faculty at Duke University Medical Center before he became Executive Officer of the Institute of Medicine of the National Academy of Sciences, Chancellor and Dean of the Medical School at the University of Massachusetts at Worcester, President of the University of Texas Health Sciences Center at Houston, and now, President of the Association of Academic Health Centers in Washington, D.C. He has published scores of papers and chapters, as well as three books on subjects ranging from infectious diseases to medical education, humanities, Hippocrates, and, not surprisingly, academic health centers. He is invited to speak throughout the world. His authority and passion come not only from his life in academia and practice. He is also a patient who has dodged a fatal bullet not only once, but, we hope, twice.

This is part two of three that will be published in The Western Journal of Medicine in November and December 1997 and January 1998. Part one was published in the November issue. What a splendid way to give thanks, to celebrate the holidays, and to start a new year. The entire book will be published by Carden Jennings Publishing Company, Inc., (1224 West Main St., Suite 200, Charlottesville, VA 22903-2858; (804) 979-8034; fax (804) 979-4025; e-mail wjm@cjp.com) and available for $10.00. Its price is low because it is partly subsidized by support from the John P. McGovern Foundation.

This book will become a classic. Eric Cassell recently listed some of his favorite medical books as he exhorted physicians to read them.[1] He noted that physicians of course need to know about the march of molecular medicine, pathophysiology, and modern diagnosis and treatment. He said that physicians also need to put patients, not just diseases or organ systems, at center stage. They need to understand health as well as sickness, souls as well as bodies, meaning as well as behavior. I would add that physicians need to know themselves, to review their values, and to refresh their energy, especially now. I would therefore endorse the following books to accompany Dr. Bulger's as we join together in the noble quest for mercy:

- *The Plague* by Albert Camus (Random House)
- *Man's Search for Meaning* by Viktor Frankl (Simon and Schuster)
- *Self Renewal: The Individual and the Innovative Society* by John W. Gardner (WW Norton and Co., revised)
- *The Way of Life. An American Version* by Lao Tzu (Putnam Publishing Group)
- *On Doctoring: Stories, Poems, Essays* edited by Richard Reynolds and John Stone (Simon and Schuster)

I hope this series will lift you as you read, reflect, recall, renew.

Linda Hawes Clever, MD

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SPECIAL SERIES—PART II

The Quest for Mercy
The Forgotten Ingredient in Health Care Reform

ROGER J. BULGER, MD, *Washington, DC*

Section II—The Bedrock of Healing

Chapter 4

Language, the Other Arts, and Scientific Healing

Having introduced the distinction between disease and illness, I have also introduced the idea that pharmaceuticals and scalpels can address diseases. But to heal the illness and begin to reduce the suffering, something else is required.

I believe that "something else" is the physician's communicating to the patient—by word, body movement, or other means of commitment—that he or she cares. This kind of communication can be rendered best by a caregiver who can decipher both the verbal and nonverbal messages that the patient conveys, and who knows how to respond to them appropriately.

It may be that some individuals are naturally more sensitive to the nuances of expression from others, and there seems to be a widespread belief that sensitivity cannot be taught. I don't believe that such biopsychosocial skills cannot be taught; nevertheless, there seems little doubt that faculty living predominantly in the biomolecular reductionist mode are often ill-prepared to either teach or exemplify such skills. Nursing curricula often address issues of interpersonal competency at practical and pragmatic levels. Physicians and dentists often are so focused on the answers to particular questions, which lead them to decisions about the use of particular interventions, that they forget about the usefulness of the open-ended question and the value of giving patients a minute or so to express themselves. This latter approach not only often uncovers crucial diagnostic information but is in itself therapeutic for the patient and may engender some peacefulness by uncovering and addressing such issues as anxiety, depression, and self-destructiveness.

Medicine: The Silent Art

Of the many forms of communication available to us, language is central to the development of the human species.* Physician Lewis Thomas identifies language as the most advanced and distinctive characteristic of our species. Cleanth Brooks, professor emeritus of rhetoric at Yale University, and I.A. Richards, a rhetorician at Harvard University, believe that language, as the medium for transmitting human value systems from generation to generation, is crucial to the development of a civilized culture. Where does medicine stand in relation to this primacy of language in the human condition?

Centuries ago, when Hippocrates and his followers revolutionized Western medicine with their insistence upon observation, accurate description, interpretation of physical events, and intelligent intervention or nonintervention based upon their understanding of the patient's status, they rejected language as an instrument for healing. An important part of that revolution is embodied in the phrase from the Hippocratic corpus which refers to medicine as the "silent art."

According to Pedro Lain Entralgo, a professor of medicine at Madrid University, Hippocrates was reacting to shamanism, ritual chanting, and the practice of ancient healers to call upon the gods to resolve whatev-

* This discussion is based on a speech made by the author at the University of Illinois Celebration, Chicago, "Emerging unities of the twenty-first century: Service as sacrament, emotional neutrality, and the power of the therapeutic word," June 4, 1992.

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er was wrong with the patient. Hippocrates called for a retreat from use of the word in attempts to heal. He wanted his followers to observe, learn, and interpret before intervening in a manner based upon their rational understanding of historical data and physical facts. The Hippocratic tradition then developed over many centuries as a stream of human activity separated from the use of the word in therapy. Doctors became doers, people of action, seeking to find new and better methods of intervening in the disease process. Talking, as a curative venue, had no place in modern Hippocratic medicine, and the dichotomy had to await Sigmund Freud for the start of some rapprochement between technique and word.

Paradoxically, in our retrospective and perhaps romanticized view of old-time country doctors, what physicians did have to offer to ameliorate suffering until the 1940s were mostly words. They personally stood by their patients, guiding them through their illnesses and advising their families on patient care.

The Power of Words

Few would challenge the idea that modern medical technology has drastically improved our lives, even though it seems at times to be overly mechanical, impersonal, expensive, and frightening. One might even contend that the "silent art" should remain evermore silent, because it is simply not cost-effective for such expensively educated medical technocrats—today's doctors—to engage in the human support function.

Changed Biochemistry

An alternative argument can be made, however, based in part upon the growing body of scientific evidence connecting the effect of a highly charged "word" on internal biochemistry. What we have begun to learn (or re-learn) about the link between the language arts and the soma suggests that physicians might well be overlooking a powerful therapeutic tool in words.

Among the modern advances in neurochemistry are many findings relating the emotional state of a person to the production of certain chemicals or secretion of certain hormones. For example, the endorphins of the brain are endogenous, morphine-like substances whose production or secretion may be influenced by a variety of external influences. A large body of research also has been conducted on the debilitating effects of depression, stress, and negative emotions on the function of the immune system. It thus becomes easy to envision how doctors could use words as therapy if they only knew how to affect the patient's emotional state in an appropriate manner. I am certain that every accomplished physician has several examples from his or her own experience.

In *The Anatomy of an Illness*, a book about his own serious illness that gave the author the opportunity to experiment firsthand with his ideas about emotions and health, writer and editor Norman Cousins provides one of the purest illustrations. He quotes Bernie Lown, a Boston cardiologist, on his treatment of a patient with an acute myocardial infarction. According to Lown, the most important therapeutic beginning can be the meeting in the emergency room between a recently stricken heart patient and an attending physician who soothes the patient by informing him or her that everything is under control: "You will be all right." Dr. Lown seldom has to administer the traditional shot of morphine to these patients, and they have taken an important initial step toward recovery. In this instance, it is clear that combining the physician's words and a trust relationship has been employed as therapy.

In a recent study, pediatrician and behavioral psychologist John Kennell and colleagues found a similar dynamic at work in the case of women beginning labor while accompanied by a supportive female companion called a doula. *Doula* is a Greek term referring to a woman who guides and assists a new mother in labor, delivery, and early infant care tasks. The doulas in the study were women who had themselves experienced a normal vaginal delivery with a good outcome, were comfortable with patients and staff from different backgrounds, and had gone through a brief training period to become familiar with labor and delivery procedures. In a controlled trial, the researchers found that the continuous presence of a doula during labor and delivery significantly reduced the rate of cesarean section deliveries (from 18 percent to 8 percent), as well as the frequency of the use of epidural anesthesia (from 55.3 percent to 7.8 percent) and oxytocin to augment labor (from 43.6 percent to 17 percent). Doula support also reduced the duration of labor and the rates of prolonged infant hospitalization and maternal morbidity.

The mechanism by which doula support influences labor, delivery, and perinatal outcome is not fully understood. Several studies in animals and humans have pointed to a link between acute maternal anxiety and disturbances in the progress of labor. It seems likely that a doula decreases maternal anxiety by her interactions with the laboring woman. Her constant presence, physical touch, reassurance, explanations, and anticipatory guidance make the laboring woman feel safer and calmer and, therefore, in need of less obstetric intervention.

Kennell and colleagues suggest that medical costs could be reduced if every laboring woman had a doula at her side. Consider the potential savings: reduced use of anesthesia and other medications, shortened hospital stays for mothers and infants, and, most significantly, reduced cesarean rates and operating-room costs. Most of these factors could also translate into enhanced well-being for new mothers and their babies.

Norman Cousins agrees that positive feelings produce positive chemical changes that have true therapeutic value. One of his experiments while he was attempting to recover from his cancer involved watching films of humorous television shows and movies. He describes the effect: "It worked! I made the joyous discovery that ten minutes of genuine belly laughter has an anesthetic effect and would give me at least two hours of pain-free sleep."

Cousins also notes the slant of "psychobiological" research, or "psychoneuroim-munology" as it has come to be called, toward the study of negative emotions and their effects on health:

> Increasingly, in the medical press, articles are being published about the high cost of negative emotions. Cancer, in particular, has been connected to intensive states of grief or anger or fear. It makes little sense to suppose that emotions exact only penalties and confer no benefits. At any rate, long before my own serious illness, I became convinced that creativity, the will to live, hope, faith, and love have biochemical significance and contribute strongly to healing and to well-being. The positive emotions are life-giving experiences.

Physician-Patient Interactions

Cousins emphasizes the importance of positive physician-patient interaction. He believes that one of the physician's primary responsibilities is to help patients fully engage their own abilities to mobilize the forces of mind and body to fight disease. Positive physician-patient interaction need not take a great deal of time; many studies note that patients perceive a one- or two-minute visit from their doctor to be much longer if their doctor sits down at the bedside rather than stand in the doorway during the visit.

Empathy

Cousins notes that empathy is an essential ingredient in a healing relationship. To stop and sit at the bedside is not only to show that you care, but also to enable you to share the patient's experience of separation from the hectic pace of activity (which we often perceive as giving meaning to our lives) and get closer to what it means to be bedridden.

Leston Havens describes the power the many forms of empathy (such as tones of voice, gestures, and facial expressions) have in knowing a person and helping that person heal. Of them all, he says, words may be the most powerful. He calls language "the engineering structure necessary to translate passion (or, a deep sense of caring) into what is clinically effective."

It is worth noting at this point that silence on the part of the physician also can be a productive diagnostic and even therapeutic tool. On the average, it is said, doctors interrupt their patients after the latter speaks for only seventeen seconds. Aaron Lazare, Dean of Medicine at the University of Massachusetts, tells me he instructs his students to give the patient a full minute and then five seconds more to speak without interruption. He then suggests a follow-up question like, "Is there anything else?"

Using empathy in healing also opens new doors to therapists by increasing their sensitivity to the feelings and needs of others. According to Havens, "To find another, you must enter that person's world. The empathic visitor then discovers what he has taken for granted in his own world: that it is a world of particular time and space."

Related to understanding how patients feel is understanding what patients think about their illness and how treatment should proceed. Cousins, along with growing numbers of health professionals, believes that sharing the decision-making role with the patient is another mechanism through which the word can exert a therapeutic effect. The word is valuable in its capacity to enhance a patient's understanding of his or her condition and to reinforce a patient's sense of self-determination; both can decrease fear and depression and their negative physiological correlates.

Cousins writes, "If I had to guess, I would say that the principal contribution made by my doctor to the taming, and possibly the conquest, of my illness was that he encouraged me to believe I was a respected partner with him in the total undertaking." Surgeon Bernie Siegel concurs: "Participation in the decision-making process, more than any other factor, determines the quality of the doctor-patient relationship. The exceptional patient wants to share responsibility for life and treatment, and doctors who encourage that attitude can help all their patients heal faster."

In an earlier chapter, I mentioned a schizophrenic patient whom I saw as a fourth-year medical student. She had earned a Ph.D. at a major university; now she babbled unintelligibly, almost as if she were challenging us to understand her rambling. Over the course of several meetings, I was able to piece together her story, one that she directed mostly at the walls and the ceiling rather than at me. She told a tale of an ancestral princess who mistakenly had been abandoned as an infant among a group of lesser beings. These clearly subordinate creatures, although frequently kind to her, nonetheless saw her as ugly and inferior. One day, the princess's true father appeared. This great king recognized his daughter and placed a magnificent crown on her head.

When she reached this part of the story, the patient suddenly looked me straight in the eye and asked, "Do you understand?" I replied, "Yes. You are that princess, your hair is the crown, the rest of us are the barbarians. But I want you to know that I respect you."

My response seemed to satisfy her need to be respected and listened to, because this moment was pivotal in our work. She improved from that point on, perhaps because she knew that I respected her and wanted to participate in her efforts to work through her shattered emotional state.

These kinds of observations, by myself and others, support the view that the physician should help the patient attain the best state of mind to cure him- or herself or to aid the external interventions in the curative process. To accomplish this feat requires a great deal of knowledge, understanding, and analysis of what makes some patients get well and others not, and how the doctor can influence the process by behavior and speech. Doctors should divest themselves of that part of the Hippocratic heritage that devalues words as restorative

tools: it is an ideology that makes it difficult for many doctors to become true healers.

Bringing About Understanding

Why have more medical practitioners not effectively employed the word in their practice? It is probably because they were never taught that words in themselves can be instruments of healing. Medical sciences teach us that x rays, hormones, chemotherapy, antidepressants, analgesics, and CAT scans are highly effective tools and that words are not. All too often, we are uncomfortable with words, embarrassed by or ineffectual with them, and we see them as valueless in the fight against a tangible physical ailment. It is a disquieting situation: as the profession becomes ever more effective in utilizing science and technology, the public is becoming increasingly disaffected by the health care received. Physicians are accused of being inhumane, mechanistically oriented, and materialistic. Although most doctors realize at some level that their words can have tremendous impact, most caregivers do not think of the use of words as a scientific mode of therapy.

As physician Lewis Thomas relates, the modern hospital environment often seems entirely incompatible with "the therapy of the word":

> Today, with the advance of medicine's various and complicated new technologies, the ward rounds now at the foot of the bed, the drawing of blood samples for automated assessment of every known (or suggested) biochemical abnormality, [and] the rolling of wheelchairs and litters down through the corridors to the X-ray department, there is less time for talking. The longest and most personal conversations held with hospital patients when they come to the hospital are discussions of finances and insurance, engaged in by personnel trained in accountancy, whose scientific instruments are the computers.

In their handbook *Talking and Listening to Patients: A Modern Approach*, medical educators Charles Fletcher and Paul Freeling point out that there is ample evidence that patients are frequently dissatisfied with what doctors tell them about their illnesses; perhaps more serious is the fact that many patients do not do what their doctors have told them to do. Various studies have shown that between 10 and 70 percent of patients (and an average of 50 percent) do not take their prescribed medications and reject their doctor's advice about changes in lifestyle.

The history of communication between doctors and patients is interesting. Many doctors used to think it was bad for patients to understand their illnesses and treatments. "Good" patients did what they were told without question. "Troublesome" patients questioned doctors in a way thought to undermine respect for, and confidence in, doctors. Although recent years have brought about a shift toward sharing medical information more liberally, many patients still find it difficult to get all the information they want to have about their illnesses. They are frequently not invited, as many would wish, to help decide on their treatment.

It is clear that there is still much work ahead. In a recent study of physician-patient communication, J. K. Burgoon and colleagues conclude that the manner in which the medical practitioner communicates with the patient may contribute more to patient satisfaction than the content of the communication itself. The authors interviewed 234 adults who had seen a primary care doctor within the previous six months. They found that greater patient satisfaction was associated with greater expressions of receptivity, immediacy, composure, similarity, and formality, as well as less physician dominance. In such consultations, patients trusted their physician more, believed the physician was concerned about them, believed they were well-informed, felt safe to disclose information, felt liked and accepted, and were more satisfied with the physician's techniques. These factors also had a modest positive effect on patients' compliance.

An Indispensable Diagnostic Tool

Not only does good communication between doctors and their patients make patients happy (and sometimes healthy), it also gives the physician the information needed to treat the patient effectively. Physician Philip Tumulty describes the dynamics eloquently:

> A clinician spends a great amount of his working hours communicating with his patients. What the scalpel is to the surgeon, words are to the clinician. When he uses them effectively, his patients do well. If not, the results may well be disastrous. . . . The wisdom of Thomas Aquinas, the logic of Newman, and the clinical genius of Osler will not be effective in making well a patient who does not understand why he is sick, or what he must do to get well.

Physician Dana Atchley echoes Tumulty's thoughts:

> Warmth and compassion break down the barriers of anxiety and fear that beset the patient coming as a stranger to the doctor, barriers that can seriously inhibit the thoroughness of a diagnostic appraisal. If a patient feels that his problems are provocative, not only of scientific interest, but also of a deep concern over his happiness, he will be more open in discussing his life and his deeper feelings, and also more cooperative in accepting unpleasant diagnostic and therapeutic procedures. A good emotional rapport between the doctor and his patient improves his efficiency as a healer and, indeed, makes the whole process more pleasant.

George Engel, professor emeritus of medicine and psychiatry at the University of Rochester, is renowned

for his definition of a biopsychosocial paradigm for medicine. He holds that, in contrast to the seventeenth century scientific paradigm (accepted by scientists like Newton, Descartes, and Curie) that portrays what is being studied as external to and independent of the scientist, what is being studied is inseparable from the scientist. At the heart of the biopsychosocial paradigm is the notion that what a scientist (or a physician) observes is not nature (or physiology) itself, but, rather, the interplay between nature and ourselves—that is, science describes nature as exposed to our way of questioning.

Engel has described the patient interview, in which the doctor is the scientist doing the studying, as the most powerful, encompassing, sensitive, and versatile instrument in all of medicine. He believes that in an encounter with a patient, the physician must operate in two modes concurrently—observational and relational. Each deals with different sorts of data. In the observational mode, the physician collects the data that can be observed through the senses (or extensions of the senses, like stethoscopes and blood pressure cuffs). In the relational mode, the physician collects data from the uniquely human realm of the interview, symbols, thoughts, and feelings. Through the relational mode, the physician learns the nature and history of the patient's experiences and clarifies what they mean to the patient and what they mean in other—psychological or social—systems. This clarification of meaning, achieved in the relational mode, illuminates measurements taken in the observational mode; together, they provide a clear, complete picture of the patient's symptoms.

Others agree that physician-patient interchange is the most potent tool for understanding a patient's illness and finding a treatment that works. In teaching medical students how to talk and listen to patients, Fletcher and Freeling divide the physician-patient consultation into two parts: the interview and the discussion, much along the lines of Engel's observational and relational modes. They emphasize the discussion mode:

> [D]octors should not just tell patients about the diagnosis and proposals for management, but should first find out their views and discuss them in order to reach an agreed diagnosis and plan of action. Studies have shown that patients will be more likely to accept and carry out this plan if they have participated in its formulation.

Fletcher and Freeling concede that good consultations may on average take more time than inferior ones, but if this means that they are more effective, they will save time in the long run.

The Language of the Fine Arts

Just as words can go a long way toward helping physicians understand people and their healing processes, so too can other forms of expression. The arts, for example, provide powerful means for communicating thoughts and feelings. Like laughter or verbal reassurance, music and painting can make people feel good—inspired, relaxed, content. The arts, too, can be a healing force.

For the physician, attempts to understand or relate to artistic works of all sorts help develop a sensitivity to patients that, in turn, enhances the ability to decipher both verbal and nonverbal messages that patients convey. After all, the arts are attempts at communication—usually of emotions and perceptions, precisely the skills in which an increasing number of patients find many modern doctors most deficient.

Psychotherapists frequently use art in therapy with young children, for whom verbal expression can be difficult. To understand their feelings better and identify possible sources of subconscious emotional conflict that may frustrate the healing process, some clinicians ask cancer patients to draw themselves, their treatment, and their disease. These drawings may facilitate treatment of patients who are ambivalent about receiving a substance that they subconsciously feel is poisonous. Once the drawing unveils the patient's subconscious resistance, the patient may be able to consciously alter his or her attitude toward treatment.

Art also can be a source of positive feelings and, hence, a stimulant to our own internal restorative mechanisms. As those who work in the arts are aware, when we create something—a painting, a sculpture, a dance—we experience the basic pleasure of bringing something to life and sharing a part of ourselves with others. In this way art is a life force, reminding its creator that he or she has the power to make things happen and is connected to others in our world. Such feelings of vitality, self-affirmation, and connectedness are precisely the sorts of feelings lost by people isolated by illness and the prospect of death, feelings that a caregiver can help to restore.

Jamake Highwater, a writer and artist, once told me that he saw humans as isolated, individual beings, who, like stars in the sky, blink silent messages to one another. To him, artists were people who are particularly adept at reaching others and thereby conquering the isolation through their art. Harkening back to the isolation of suffering, connecting with an artist can be viewed as good for patients as well as for doctors who need practice in successful communication.

The therapeutic value of art is gaining increasing recognition. Programs to bring artists-in-residence to health care facilities have been created, and a field called "health care arts administration," in which hospitals become patrons of art for its therapeutic value for patients, has taken shape. Architects of newer hospitals have designed them to be brighter, more airy, and painted in pleasing pastels; their hospitals feel more like places for healing than places for isolating the sick or dying. Research has confirmed that patients are measurably better off if their room has a window offering a natural view. As pathologist and biomedical scientist Guido Majno points out, it is difficult to rise above the daily routine when the eye cannot catch a glimpse of the sky.

The Language of Music

The expressive and healing properties of music are perhaps the most widely recognized among all the arts. Music therapy is an established health profession; its beginnings, according to music therapist John Beaulieu, can be traced back to the observations of a group of professional musicians who worked with returning World War II veterans. The musicians volunteered in hospitals with the intention of helping the veterans pass time pleasurably. To their surprise, the musicians began to notice that the patients who were regularly exposed showed a marked increase in morale, as well as improved socialization skills. As their suppressed emotions found a safe form of expression through music, their depression lifted faster.

The National Association for Music Therapy, in Washington, D.C., and the American Association for Music Therapy, in Springfield, New Jersey, are two professional associations dedicated to understanding the healing qualities of music and sound. Founded during the 1950s and 1960s, they certify music therapists graduating from the more than seventy university training programs in music therapy; they also support research and work to increase public awareness of the benefits of music therapy. Today music therapists work in hospitals with such populations as the mentally retarded, physically handicapped, and learning disabled, as well as with people suffering from cancer, heart problems, and psychiatric conditions.

Norman Cousins relates the experiences of two famous personalities with illness and music. One was cellist Pablo Casals, who experienced infirmities in his late eighties; when he turned to his instrument, he breathed more easily, his fingers unlocked, and his back seemed to straighten naturally. Casals described his relief:

> I see Bach as a great romantic. His music stirs me, helps me to feel fully alive. When I wake up each morning I can hardly wait to play Bach. What a wonderful way to start the day. . . . I suppose that every musician feels that there is one piece that speaks to him alone, one which he feels seems to involve every molecule of his being. This was the way I felt about the B-flat Quartet ever since I played it for the first time.

Cousins also cited the experiences of the great missionary physician and theologian Albert Schweitzer:

> Johann Sebastian Bach made it possible for [Schweitzer] to free himself of the pressure and tensions of the hospital. . . . He was now restored to the world of creative and ordered splendor that he had always found in music. . . . He felt restored, regenerated, enhanced. When he stood up, there was no trace of a stoop. Music was his medicine.

In the 1980s, the University of Texas Health Sciences Center at Houston developed a program to bring the visual and performing arts to the center. I recall attending a brown-bag lunch in a medical school classroom at which the director of a local professional ballet troupe discussed preparation for the troupe's performance at the school the next day. I know nothing of ballet and am not a lover of the dance. Nevertheless, I learned more in that half hour about body language in particular, and nonverbal communication in general, than I had in twenty years of clinical and teaching practice.

The troupe director demonstrated the way in which her completion of a movement or gesture sent messages to the audience, and explained how certain movements could elicit an audience response . Since then, I have become more adept at reading body language. I have also gained a new and apparently lasting awareness of how I use my body language with other individuals or with groups.

The Art of Healing

With regard to the development of a healing relationship or the use of words or other forms of communication as therapy, I feel certain of two points:

1. It is a humbling subject, which can engage any interested caregiver for a lifetime of learning and self-enhancement.

2. The ability to succeed at helping others help themselves ease their suffering or defeat their disease has everything to do with caregivers building trust and confidence in the patient, accepting the patient and the patient's predicament in a nonjudgmental way, and sticking with the patient until the situation is resolved. By what he or she does or says, the caregiver must demonstrate that she or he cares for the patient.

Thus, whatever interaction one can have and enjoy with language, art, music, and other forms of communication can only enhance, either directly or indirectly, one's capacity to be a consistently constructive, positive force in a patient's life. It all boils down to the so-called "art of medicine." Successfully communicating a sincere interest in improving the patient's condition helps the patient feel more comfortable from the start. The very act is "healing," both for the caregiver and the patient.

Chapter 5

Treating Disease and Curing Illness

Oliver Wendell Holmes, in the nineteenth century, said, in effect, that if all the medicines in the world were thrown into the sea, it would be bad for the fish and good for the people. A famous French physician of that same era is also said to have stated that it was important to use all new treatments as often as possible before they became ineffective. L.J. Henderson, the Harvard biochemist, is reputed to have stated, "Somewhere between 1910 and 1912 in this country, a random patient, with a

random disease, consulting a doctor chosen at random, had for the first time in the history of mankind a better than fifty-fifty chance of profiting from the encounter."

The Placebo Lesson

Clearly, medicine has had its trials as well as its triumphs. Given the historical ineffectiveness—and in some cases, danger—of medical treatments and procedures, what can account for the constant need, use, and perceived success of medicine throughout the centuries? The answer may be found in a review of placebos.

A. K. Shapiro defines a placebo as

> Any therapeutic procedure (or that component of any procedure) which is given deliberately to have an effect, or unknowingly has an effect on a patient, symptom, syndrome, or disease, but which is objectively without specific activity for the condition being treated. The therapeutic procedure may be given with or without conscious knowledge that the procedure is a placebo, may be an active (noninert) or nonactive (inert) procedure, and includes, therefore, all medical procedures, no matter how specific.

The placebo *effect* simply refers to the outcome, favorable or unfavorable, that a placebo produces in the person who takes it. Herbert Benson and David McCallie, both of whom are physicians and physiologists, point out that the placebo effect may be subjective or may have objective physiologic manifestations. These manifestations can include an increase in endorphins, which leads to a reduction in pain. Higher endorphin levels also lead to increases in the vitality and effectiveness of the immune system's T-cells and macrophages, which can directly ameliorate and sometimes cure disease. Benson and McCallie describe three factors around which the placebo effect tends to revolve: the beliefs and expectations of the patient, the beliefs and expectations of the physician, and the nature and quality of the physician-patient relationship. They argue forcefully for more research on the placebo effect based on its powerful potential to affect patients' health.

A recent survey of the literature by psychiatrist Judith Turner and behavioral researchers supports the placebo potential. They found that placebo response rates vary considerably and are often much higher than the frequently cited 30 to 40 percent. They also point out that placebos tend to have time-effect curves, with peak, cumulative, and carryover effects that resemble those of active medications. Interestingly, Turner and colleagues also note that individuals tend to be inconsistent in their placebo responses and that no "placebo-responder" personality has been identified. Their article is a useful resource on the critical role that the placebo effect plays in the evaluation of new medical treatments.

More and more, developments in modern neurochemistry, neuroendocrinology, and neuropsychoimmunology allow us to envision how, at a molecular level, emotions and beliefs can influence everything from white-cell function to cardiovascular events. It has become much easier to consider the art of medicine as an emerging science through which the adept practitioner encourages the patient's own internal pharmacy to dispense agents in therapeutic combinations and amounts at just the right time.

The Placebo Effect

The essential mechanism of the placebo effect resides in the intersection of belief with pathophysiologic and molecular biologic processes. Simply put, a physician gives a patient with a complaint an inactive pill, and the patient takes the pill, believing that it will relieve his or her symptoms. And it does. Not limited to treatment in the form of pills, the placebo effect can occur after any treatment, even surgery, that the physician and the patient believe is effective.

A number of studies on placebos and the placebo effect illuminate this fascinating link between psychological and physiological processes.

The first set addresses the phenomenon of voodoo death or "bone-pointing." The most interesting is a long essay by Walter Cannon, published in 1942 in the anthropology literature. Cannon describes instances of deaths among primitive peoples that truly seemed to result from the spells, sorcery, and black magic dispensed by "medicine men." Cannon brings unquestionable scientific credentials as a modern physiologist obviously sincerely interested in his research, and it is difficult to come away from the essay without acknowledging the probability that these mysterious deaths (mysterious, at least, to Western observers) did indeed occur.

Cannon described the bone-pointing syndrome as rooted in the tribal members' belief that they will die if a certain bone is pointed at them. The syndrome, which involves a rapid decline in health and then death, is initiated when a person of authority points the bone at an individual, or when an individual becomes aware that a punishable transgression deserving the bone has occurred. Death is surprisingly rapid even in previously healthy individuals. No intervention of Western medicine was observed to alter the downhill course of the syndrome, and no disease could be identified to explain the symptoms.

Cannon told of the case of a perfectly healthy young Maori man who began to die when he became convinced that, two years previously, he had been tricked into eating a forbidden food that was purported to cause instant death. Following this realization, the young man traced a rapid path downward, neither eating nor speaking. His Western friends tried everything to reverse the course of events, but their efforts were to no avail. Finally, they found the young man's tribal medicine man and bribed him to tell their friend that the gods had revoked the prohibition on the food he had eaten and that the spell had been removed. Near death by all physiological measures, the young man immediately brightened, began to eat and talk, and soon completely recovered.

Self-effected deaths have been observed in this country as well. For example, many clinicians recognize as almost commonplace the death of the remaining spouse shortly after one member of a long-married pair passes away. Modern articles on this subject have been written by George Engel, who studied rapid death during times of psychological stress, and G. W. Milton, who studied self-willed death in patients with melanoma.

Another set of relevant studies by researcher Stewart Wolf and his colleagues focuses on the placebo effect in gastrointestinal physiology and pharmacology. In one study, Wolf used pressure-recording devices to study gastric contraction patterns in several human subjects at rest, during digestion, and in times of nausea and vomiting.

In subjects stricken with nausea and vomiting, he was able to show that the administration of ipecac, a medicine that induces vomiting, had different effects based on the information given to subjects. When subjects were openly given ipecac, they vomited as expected. When the subjects were told that they were receiving an agent that would relieve nausea and prevent vomiting, their symptoms abated even though they had received the ipecac. Wolf concluded:

> Placebo effects which modify the pharmacologic action of drugs or endow inert agents with potency are not imaginary, but may be associated with measurable changes at the end organs. These effects are at times more potent than the pharmacologic action customarily attributed to the agent. Thus the familiar difficulty of evaluating in patients new therapeutic agents stems not only from inadequately curbed enthusiasm of the investigator, but also from the actual physiologic effects of their "placebo" action.

In a subsequent study, Wolf and M.A. Pinsky studied the effect of an agent purported to reduce anxiety and tension in thirty-one patients with a variety of chronic disorders, all with a heavy overlay of symptoms related to anxiety and tension. Each patient was alternately given a placebo and the test agent in a manner blind to both patient and physician. The researchers found that regardless of whether the treatment was the test agent or the placebo, about 15 percent of the patients got better, 70 to 75 percent stayed the same, and 10 to 12 percent got worse after each treatment.

Many of the subjects had vague and nonserious symptoms. Three had major reactions. One had overwhelming weakness, palpitation, and nausea within fifteen minutes of medication, regardless of whether the treatment was the test agent or the placebo. A second patient developed a diffuse, itchy rash after ten days of medication; when the medication was stopped, the rash disappeared, and the patient refused to participate further, even though the rash had occurred as a result of a placebo administration. The third patient experienced several symptoms, including watery diarrhea, within ten minutes after taking the pills; this patient experienced the same symptoms on three separate occasions after taking the pills, which turned out to include the placebo. These findings point to the power of the mind to effect real, and sometimes dramatic, physical symptoms.

A set of studies focusing on the relationship between psychology and physiology is summarized in a 1989 research briefing published by the Institute of Medicine of the National Academy of Sciences. The report concludes that substantial scientific evidence exists that behavior influences the immune system, both directly and through the endocrine system. The report relates the finding, for example, that bereaved men exhibit a decrease in immune system competence immediately following the deaths of their wives.

Others have uncovered similar connections. Researchers Janice Kiecolt-Glaser and Ronald Glaser, in their study on psychological influences on immunity, reveal the relationship between stressful life events and changes in the strength of the immune system. Neuroscientist Candace Pert and her colleagues build a case for the existence of a communications network of chemical interactions mediated by neuropeptides and their receptors, which join the endocrine glands, the brain, and the immune system in what amounts to the "biochemical substrate of emotion."

The patient's faith in the doctor, not in the pill, seems to be the most powerful force operating in the placebo effect. Bernie Siegel describes the role of the faith healer in primitive medicine and the somewhat analogous role of the modern Western physician as a source of inspiration for self-healing:

> Nearly all so-called primitive medicines use the placebo factor via rituals that foster assurance in the healing force, whether it is defined as an external god or an internal energy. Faith healing relies on the patient's belief in a higher power and the healer's ability to act as a channel to it. Sometimes a mere artifact or saint's relic is conduit enough. For a believer a bottle labeled Lourdes Holy Water has healing properties even if there's only tap water in it. . . . This is why it's so important that a physician have . . . the ability to project confidence. A patient's hope and trust lead to a "letting go" that counteracts stress and is often the key to getting well.

Debate About Placebo Use

Why then, when many studies on the placebo effect suggest that placebos lead to a 30 to 40 percent (some claim 50 or 60 percent) improvement rate in almost any symptom, has this important tool been ignored for so long?

Since the Second World War, what we may appropriately call the biomolecular revolution has swept forward with dramatic results, touching virtually all of our lives. The words "one gene, one enzyme, one protein, one disease, one precise cure" describe the concept of reductionist biomedicine at its best. This paradigm has produced increasingly effective tools, which have been so dramatic that all of us have focused on the tools and not on the

healer or the healed. The Human Genome Project, which for the last decade has progressed ahead of schedule in its effort to map the entire human genome, with all the incredible potential it entails, is perhaps the ultimate expression of the reductionist theory.

Generations of doctors have been trained under the pervasive influence of the tremendous successes of the biomolecular revolution, which seems to extend the promise of perpetual improvement. In that context, physicians have come to regard placebos and the placebo effect in a cavalier manner, if not with outright disdain. Many mature physicians consider that a patient cured by placebo is somehow something less than a "real" patient and that a doctor whose work is done through the placebo is less than a "real" doctor.

It is true that Americans have a strong belief in high technology. We believe in our capacity to control or intervene artificially in nature. Our faith in interventionist technology should be challenged by the abundant and increasing evidence that most acceptable and standard medical practice consists of interventions whose effectiveness has not been statistically proven. Recent exploration of the placebo effect in and of itself has probably had a positive impact on the health of patients by placing renewed emphasis on the quality of the physician-patient interaction. Physician Howard Spiro describes this impact:

> [W]e physicians live in two worlds: the world of science, which provides us with our ideals and with the real advances against disease, and the world of people, persons with instincts, with pain, suffering, hope, and joy. We have a hard time separating out what we learn in science from what we need in practice to deal with people. The placebo reminds us to focus on the interface between those two worlds.

Spiro adds, "What the placebo effect does is to act as the symbol of a connection—tangible evidence that some person cares and will try to do something."

In a recent issue of the *Annals of Internal Medicine*, William Zinn reports on the transference phenomenon in the physician-patient relationship and its power to affect health:

> Transference is a process in which individuals displace patterns of behavior that originate through interaction with significant figures in childhood onto other persons in their current lives. It is a powerful determinant of patient behavior in medical encounters. Transference can affect the kind of physician-patient relationship a patient seeks and his or her response to interventions prescribed by physicians. . . . Transference issues can also affect level of somatization and patient adherence to medical regimens.

Some have expressed concern about complications that placebo use may introduce into the caregiver-patient relationship. Author and lecturer in philosophy Sissela Bok argues categorically that giving a placebo to a patient constitutes an overt act of trickery and, however well intentioned, constitutes an unethical act. She refers largely to situations in which doctors give patients "sugar" pills or other inert substances, claiming that the substances are medication. If our understanding of the placebo effect is broadened, however, to take into account that it can occur with any therapeutic intervention involving either inert and active substances, then the physician giving medicine with an obvious hope that it will improve the patient's condition clearly seems acceptable.

As debate about the ethics of placebo-use persists, other potential problems posed by placebo treatment are clear. Spiro describes some of the practical hazards of placebo use by physicians; one of the most serious is that physicians may delude themselves into thinking that their patient has no significant disease because it was a placebo that successfully relieved the patient's pain. The physician may also mistakenly conclude that a placebo response means the original complaint was feigned. In either case, successful placebo treatment can engender false security or complacency in future instances of disease in a particular patient. In my own view, deliberate use of inert substances as placebos is a serious threat to the integrity of the clinician-patient relationship and should be avoided.

Learning More About the Mind-Body Relationship

In sum, we seem to have come full circle. Our modern science has generated spectacular new technologies, many of which are commonly accepted but largely unproven in terms of effectiveness, especially in comparison to the placebo effect or to other, perhaps less costly, interventions. Frequently, these technologies are practices in which physicians—and the public—place faith. Some future anthropologist may well conclude that our current American health care system is merely a high-tech, highly interventionist, specialty-oriented enterprise that is actually a giant, super-sophisticated, highly mechanized placebo. If so, we must sustain at least the 40 percent effectiveness of the placebo effect and not squander the public trust, thereby reducing this success rate. On the other hand, no reasonable person doubts the wonderful contributions of modern science to diagnosis, therapy, and prevention. Our evolving sciences show every sign that our laboratories will continue to issue truly effective therapies. Equally important is using our science to learn all that we can, as quickly as we can, about the mind-body relationship. If we can

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AUTHOR'S NOTE: A patient's faith in the doctor can also produce negative effects. Critically ill patients, for example, often ask their doctors how much longer they can expect to live, and their doctors often consider the odds and come up with a number. In many cases, patients who trust their doctors die right on schedule, as if to validate their doctor's prediction, even when, given their actual physiological condition, they might have lived longer. In light of this phenomenon, many observers believe that physicians make a serious mistake when they yield to the temptation to give such time prognoses.

understand how an individual's beliefs can enable the patient, and not the doctor, to effect a cure, then we have hit on real healing that could provide us with the means to teach others how to heal themselves.

Chapter 6

Death and the Caregiver

There was a soft gurgle, followed by a gush of clear fluid that poured out of her mouth and onto her chest.

"She's dead," I thought. "My first death."

The intern standing next to me, in his second week at the Boston City Hospital, rushed off confusedly to try to do something about it. She was his patient. She was dead. The year was 1960 and I, a fourth-year medical student with no ultimate responsibility, actually accepted the fact of her death before the intern did. It was an awesome experience. I had finally witnessed that which all medicine is aimed against.

Like most of us, I wanted never to lose my respect and sense of awe for death. I vowed that at each subsequent deathbed I would recall, or try to recall, some of the feelings that had moved me this first time.

One week later, we students on that rotation rushed down the ward to the bedside of an apneic, cyanotic, cardiac patient, aged 65. An intern was thumping the patient's chest. I tried to figure out what I would do next were I the intern. The epinephrine was injected into the patient's heart. I was waiting and hoping for my first open thoracotomy. But the intern decided against the emergency procedure.

I was disappointed. The patient's heart had stopped; if he had held out a few minutes longer, there might have been a thoracotomy.

Another student ran to get an ophthalmoscope to try and see what was happening in the fundi at the hour of death. My interest picked up again. He returned and looked in. Then it was my turn. Zealously, I pulled back the dead lid, satisfied in my pursuit of knowledge, happy with my intellectual curiosity. I focused the ophthalmoscope and then saw, realized, remembered what I was doing.

It is a curious fact that future physicians spend countless hours learning about life and how to preserve it; learning about diseases and how they can kill people; and yet manage to avoid thinking about death as easily as the next person. Surely, we are young; we have not really entertained the thought of not being. Nevertheless, it seems appropriate that we (the students), in some sense should be experts about death, and that we not misinterpret that eleventh medical commandment: "Thou shalt not get emotionally involved with your patients."

Our society, rightly or wrongly, for better or for worse, predisposes us to the position that death is the ultimate evil and to be avoided at all costs.

I wrote the above words many years ago. The occasion of witnessing death for the first time creates vivid images; my recollections remain with me to this day. Interestingly, in the four decades since I wrote these words, the personal impact of a medical student's—indeed, any person's—first experience with death has probably not changed a great deal.

The tenet that doctors not get emotionally involved with their patients still also persists, as does the belief that the point of medicine is to eradicate death. But the winds of change, or at least a gust here and there, have appeared.

Let us see if some of my words of 1960 reflect aspects of medicine today.

It is obviously crucial to teach medical students the intricacies of every method or technique that might possibly bring someone back from extremis. It is vital that no potential life-saving step be overlooked, but it does seem somewhat symptomatic that few words, if any, have ever been spoken to us about how to help a [person] die. It is our duty to see that s/he dies "in balance," but no one has ever suggested that we ought to make an attempt to care for her/his psyche during her/his last hours. We all believe that it is poor medicine not to "treat the whole patient," and furthermore we will expend a great deal of energy in enhancing physical comfort in small ways, which may have no influence on the final outcome of the sickness—and yet it is not always noticed that a dying man or woman very often seems to have less attention paid to them than to the patency of the multiplicity of tubes that are entering them from every direction, and which will enable us to study posthumously their last, hopefully balanced, chemistries.

It is not always noticed that more real effort is expended to get autopsy permission than to see to it that the patient does not die alone. It is almost as though, as doctors, we express our denial of death by focusing our attention upon the tubes, the chemistries, and the autopsy.

We tend to regard our treatment as having failed if the patient dies. "Successful treatment" is a term too often reserved only for those who live. One could submit another category, that of the successfully treated terminal event. One could suggest that the physician throw off her/his scientific mantle when at the deathbed, and become something else—and that something ought to be whatever the patient requires. It is apparent that, for a physician in modern America to do this, he must be capable of dealing sympathetically with agnostic, atheist, Protestant, Jew, Moslem, or Catholic, and with what he may consider personally to be unreasonable, superstition, or sheer lunacy.

It is hard for a student to talk about this ability in a physician because it seems that experience, both external and internal, as well as sincere effort are needed before one can succeed in becoming expert (if indeed one ever can) at helping the dying person through her/his death. Here, if anywhere, is the greatest stronghold of the practice of the art of medicine; here, as in every other area of medicine, is what one accomplishes proportional to what one offers; here, too, is what one offers proportional to what one knows.

The Wounded Healer

In some senses, the death of a patient is an insult or setback to the physician. In his book, *How We Die*, physician Sherwin Nuland considers what factors may underlie this perception: "Doctors are people who succeed—that is how they survived the fierce competition to achieve their medical degree, their training, and their position. Like other talented people, they require constant reassurance of their abilities."

Feelings of failure when a patient dies, even when the death is largely inevitable, may be responsible for this "wounded healer" syndrome. Doctors as a group suffer from stress far more than most other members of society and are more likely to have problems with chemical dependencies. In his best-seller *Love, Medicine, and Miracles*, Bernie Siegel writes:

> Throughout our training we learn not to empathize with the sick, supposedly to save us psychic strain. . . .The emotional distance hurts both parties, however. We withdraw just when patients need us most. Nurses know how hard it is to find a doctor when a patient is dying. All our education encourages us to think of ourselves as gods of repair, miracle workers. When we can't fix what's broken, we crawl off to lick our wounds, feeling like failures. The distance also encourages doctors to feel invulnerable: "It's always other people who are sick, not me." When I tell a roomful of medical students, "Almost everybody dies," they all laugh; but when I say the same line to a roomful of doctors, there's dead silence. We become the best deniers of all.

However, whether a patient is terminally ill or faces a serious risk of dying in surgery, it is beneficial for patient and health care team alike, physicians included, to recognize, accept, and even discuss the possibility of death.*

As an intern, I cared for a tough, elderly, white man from Montana who had a serious cardiac condition. Without treatment, he could expect his health to deteriorate gradually to where he would have to assume a sedentary lifestyle far different than the one he was used to on his farm, and then face a premature death. Open-heart surgery, on the other hand, could significantly improve the quality of his life or, just as easily, end his life. The patient chose surgery, and briefly returned home to Montana to put his affairs in order.

On the morning of the surgery, I stopped by to wish him well. Tears filled his eyes as soon as he saw me enter the room; I could barely extend my good wishes before escaping into the hall where I, too, began to cry. This episode made me realize that I had become so emotionally involved with this patient that it would not be appropriate for me to be part of the surgical team. Striking a balance between human compassion and clinical detachment is a challenge for health care professionals as they strive to accept that death is the natural endpoint of life. It is not easy.

The idea that doctors should try everything to keep the patient alive, even if being alive entails suffering further agony as inevitable death makes its way, is pervasive. Our increasing control over the timing or occurrence of death has positive implications for patients able to return to lives of quality, but it can also bring about frightening, painful, and prolonged death. In many cases, our technology has outpaced our spiritual understanding of death and our compassion for dying patients.

In addition, the environment for malpractice in our litigious society may motivate doctors to pursue every method of sustaining life, even when that course of action may be harmful to patients and to themselves alike. Nuland describes the dilemma posed by the almost endless array of technological treatment options:

> Pursuing treatment against great odds may seem like a heroic act to some, but too commonly it is a form of unwilling disservice to patients; it blurs the borders of candor and reveals a fundamental schism between the best interests of patients and their families on the one hand and of physicians on the other.

Physician Timothy Quill writes of this same dilemma:

> When the possibility for meaningful recovery becomes remote, then burdensome treatment begins to feel more like torture than a difficult means to a higher purpose. If the decision makers successfully shield themselves from the true burdens of treatment or from the reality that a patient is dying, then medical treatment can unintentionally prolong and dehumanize the dying process.

Just as aggressive treatment in the face of inevitable death may give patients and their families false hopes or "cheat" them out of a more peaceful parting, it can also be demoralizing to physicians.

Nuland defines the drive of many physicians to understand the precise details of a patient's pathophysiology, make a diagnosis, and design and carry out a specific cure—sometimes without regard to the well-being of the patient—as "The Riddle." He writes:

> The satisfaction of solving The Riddle is its own reward, and the fuel that drives the clinical engines of medicine's most highly trained specialists. It is every doctor's measure of his own abilities; it is the most important ingredient in his professional self image. . . . A physician's driving quest to solve The Riddle will sometimes be at odds with our best interests at the end of life.

It is interesting to note that societal and patient perceptions of doctors can also energize the quest to solve The Riddle. People tend to believe that doctors' reasons

* On the basis of all I believe I know about the nature of the healing relationship, however, it would be a serious error to make physicians the agents of death.

for recommending certain courses of action are wholly scientific. It is easy to overlook some of the other motivations, such as the doctors' need to preserve their own image as healers and conquerors of disease, that may be at play in doctors' medical decision making.

Let us continue with my words from more than thirty-five years ago:

It is clear that we ought to be familiar with the concept that death is a cruel and utter end to some people, while only a transition to something better or worse to others, and that we ought to be willing to act accordingly in our relationships with our patients. It is also obvious that any consideration of death does become philosophical and theological, and is, therefore, rather subjective. . . . But there must be something more we can know, objectively, collectively, to sharpen our sensibilities, deepen our insight, broaden our background, and thus enhance our understanding of any given patient in his last hours.

Evolving Perceptions of Death

An interesting historical account of evolving perceptions of death appears in a book by ethicist Daniel Callahan. Callahan relates how death used to be a familiar, steady, and routine part of daily life. It frequently took place in the home, amidst family and friends who gathered to give meaning to the dying person's final moments and, as Callahan supposes, to show communal solidarity in the face of death. Prior to the rise of scientific medicine in the eighteenth century, medicine could do little to alter the course of critical illness, and death from illness was an openly accepted part of life.

With scientific medicine has come new medical tools and increased life expectancies. New beliefs about death also have begun to take shape; people no longer see death as a fixed, collective destiny, but as a personal tragedy, preventable or at least delayable. Where death was once a public event, it is now a private event, somehow ugly or shameful. People feel the need to sanitize the experience; families have begun to take their dying relatives to hospitals and nursing homes to die. Doctors often lie to dying patients to spare them the agonizing anticipation of death. In all of society, death has become a topic that is rarely discussed.

Although we have begun to explore the meaning of death in our modern society and to wonder whether we have perhaps made coping with death more difficult by shrouding the event in secrecy, we have yet to integrate death fully into our collective psyche despite its inevitability. Callahan writes:

> Death has not come out of the closet; only its foot is showing. . . . For all of its great triumphs, contemporary medicine does not know what to make of death. The end of life represents a troubling, and particularly recent, vacuum in its thinking. Death has no well-understood place in medical theory, even if it remains omnipresent in practice.

The Rescue Credo

The anxieties and ambivalence of the public and the medical profession over the handling of death feed one another, and technological advances continue to cloud the situation by proffering a myriad of technologies that can prolong and even substitute for many of the body's physiological workings. Callahan continues:

> There may even be a rising degree of anxiety about dying based on the growing difficulty in making a clear determination that a patient is dying, and that nothing more of life-extending benefit can be done. It is exacerbated by a widespread fear that modern medical death can strip a person of choice and dignity.

It is not merely the availability of new medical technologies that has complicated issues around death. Perhaps more important is the coupling of this availability with a belief that new technologies must be maximally employed, a belief that has been called the "rescue credo" of high-tech medicine. This credo is particularly influential when the patient's prognosis or wishes are unknown; in such cases, the credo dictates that physicians err on the side of aggressive medical treatment. As Timothy Quill explains, the rescue credo has its origins in emergency medical care, and he suggests that is probably where it should stay:

> There is a "presumption to treat" in medical care that protects physicians if they initiate emergency, potentially life-saving medical treatment in good faith on a patient in an emergency without the patient's knowledge or prior agreement. However, the presumption that all patients consent to medical treatment when their wishes are not known must be rethought in the case of the severely ill and the dying. Many times medical professionals feel forced to continue invasive medical treatments on patients whose wishes cannot be inferred with certainty, even when the effectiveness of such treatments is poor and the burdens are high.

Easing Out of Life

The medical mandate to prolong life clearly has its place, especially when aggressive medical treatment is likely to lead to a healthy, happy existence for the patient. In other cases, however, the value of the rescue credo must be critically evaluated. Patients unquestionably have the right to fight for life even when the odds are poor. But they should not be pressured to endure interventions that may prolong life while, at the same time, increasing physical or emotional suffering. Some would criticize those patients who do not elect to undergo every procedure that might buy another few days of life. Quill censures this as a harsh puritanical approach to fighting death that seems to pervade current medical thinking. "Going 'gentle into that good night' with one's dignity and sense of self

intact," he argues, "is certainly as morally acceptable as raging 'against the dying of the light.'"

Despite the fact that the fear of lawsuits has added impetus to the rescue credo, physicians and other caregivers are increasingly appreciating the value of confronting death openly and of carefully evaluating the benefits and burdens of aggressive medical treatment. Many recognize psychiatrist Elisabeth Kübler-Ross as one of the first to break ground in this area with her 1969 book *On Death and Dying*. Kübler-Ross espoused dealing with death and the dying patient sincerely and compassionately; her candid perspective is reflected in her own description of the book:

> It is not meant to be a text book on how to manage dying patients, nor is it intended as a complete study of the psychology of the dying. It is simply an account of a new and challenging opportunity to refocus on the patient as human being, to include her-him in dialogues, to learn from her-him the strengths and weaknesses of our hospital management of the patient. We have asked her-him to be our teacher so that we may learn more about the final stages of life with all its anxieties, fears, and hopes. I am simply telling the stories of my patients who shared their agonies, their expectations, and their frustrations with us. It is hoped that it will encourage others not to shy away from the "hopelessly" sick but to get closer to them, as they can help them much during their final hours. The few who can do this will also discover that it can be a mutually gratifying experience; they will learn much about the functioning of the human mind, the unique human aspects of our existence, and will emerge from the experience enriched and perhaps with fewer anxieties about their own finality.

The Hospice Movement and Comfort Care

Kübler-Ross's work was followed closely by the hospice movement in this country. Patterned after the efforts of Cicely Saunders, physician and founder of the hospice movement in Great Britain, the movement seeks to provide peaceful, caring environments without aggressive medical treatment for patients facing death. Hospice care takes place in special facilities (hospices) and, probably more often, in home care programs. A multidisciplinary team of professionals, including physicians, nurses, social workers, volunteers, and clergy deliver the care, often in concert with a patient's family members. Hospice programs have proliferated in the past twenty years, and in the mid-1980s they qualified for support under Medicare.

At the heart of hospice is what has been called "palliative" care or "comfort" care. Comfort care is a humane approach to the medical treatment of incurably ill patients that focuses more on quality of life, personal desires, and symptom alleviation than on prolonging life or treating disease. Although comfort care is most commonly associated with the hospice movement, it can be used in any clinical setting.

Unfortunately, comfort care is usually offered quite late, if it is offered at all—only after all possible effective treatments have been exhausted and the patient is near death. The care is usually presented apologetically (as if the physician has failed to help), rather than positively, as a legitimate and valuable approach to the last days of life. Comfort care is not frequently explored with patients whose quality of life is deteriorating and for whom acute medical treatments are increasingly arduous. Quill explains why: "For some physicians, the comfort care philosophy threatens deeply held traditional medical values. Many see their primary mission as fighting for life, and easing the passage to death has no place in that fight."

Many people who have studied death have observed that physicians sometimes even abandon dying patients for whom there are no more technological options. It seems likely that physicians remove themselves from the patient's bedside out of discomfort with death and their helplessness to stop it. Nuland relates this abandonment to The Riddle:

> As long as there is any possibility of solving The Riddle, [physicians] will keep at it, and sometimes it takes the intervention of a family or the patient himself to put an end to medical exercises in futility. When it becomes obvious, though, that there is no longer a Riddle on which to focus, many doctors lose the drive that sustained their enthusiasm.

To some extent, the problems of abandonment and oversight of comfort care options are probably rooted in the experience of medical education. On this point, Quill notes:

> In teaching hospitals, most patients are no longer seen by medical students or residents when the decision is made to treat them with comfort care. It is felt to be a waste of the trainee's valuable time when they are "not going to do anything." "Not doing anything" translates into not undertaking traditional, disease-oriented medical treatments; but by implication it devalues the many complex medical options still available to comfort the terminally ill. The clear message is given that caring for the dying has less importance than caring for those who will use medical technology to fight for life.

Nevertheless, it is certain that many mature clinicians know well the art of helping patients and their families negotiate the uncertain shoals of a certain death, without exposing everyone involved to expensive, uncomfortable, and ultimately futile interventions, and a number of hospitals have recently endeavored to develop ethical and compassionate protocols for providing care to terminally ill patients.

For example, Texas's Hermann Hospital has developed a Supportive Care Protocol through its Program on Humanities and Technology in Health Care, led by

physicians Stanley Reiser, Lawrence Tancredi, and Cheves Smythe. The protocol establishes clear guidelines for implementing decisions concerning supportive care for terminally ill patients. It specifically recognizes that "patients and their families (or other surrogate decision makers) may make decisions about health care that include changing, limiting, declining, or discontinuing a particular treatment, whether life-sustaining or otherwise."

The protocol stresses that "the hospital's philosophy is to promote and protect patient dignity in the face of impending death by instituting medically appropriate care. Comfort will be maintained at all times through the provision of analgesics, hygienic care, and other appropriate medical and nursing care to all patients."

Protocols such as these reflect the medical establishment's increased willingness to deal with death and issues about dying patients. Medical schools have also made some progress in their approach to death. Many offer classes on death and dying, and a large body of literature has grown on the subject. The idea that the study of death could benefit from an emphasis on the meaning of death for individuals and societies, instead of on its physiological correlates, has received increasing support in the last three decades.

Finally, the American public is taking more interest in dealing openly with the subject of death and the unnecessary prolongation of life. Living wills, advance directives, and health care proxies, all of which give people greater power of self-determination, also represent positive steps toward our society's acceptance of death. The recent exploration of death in the popular press, particularly Nuland's *How We Die*, exemplifies the tentative steps we are taking back to a view of death as part of a natural progression of life.

Despite this progress, much remains to be done. As the Dax case clearly shows, the refusal of the health care team to listen and to honor a dying or seriously injured person's express wishes remains common. The behavior of Dax's health care team is mirrored, to some extent, in the current debate over the propriety of physician-assisted suicide. We, as a society, have yet to decide that we will view death as a natural and inevitable occurrence, and that we will simply offer the dying the opportunity to depart this life in as humane and dignified a manner as possible.

Committing to the Patient

Physicians, nurses, and other health care professionals should try to understand better the social and psychological aspects of death, and perhaps even some of the unconventional approaches to care that some find therapeutic. In this way, they can develop a more humane approach to caring for the dying. Good communication skills are essential to understanding a patient's wishes. Implicit in this two-way exchange must be a sensitivity to the value of patient desires in formulating treatment protocols whether or not those wishes are for aggressive intervention or comfort care. Encouraging patients to complete advance directives is one context in which physicians can initiate discussion about death and dying with their patients. Perhaps more important is the fact that advance directives relieve the ambiguity that can make death and dying in a medical setting so ominous.

Physicians must also explore their own beliefs about death. This self-reflection can help relieve personal anxiety about death. Perhaps more important, it can also enable the physician to neutralize more easily any overriding influence that the physician's personal values may have on treatment decisions that truly belong to the patient or the patient's family. Having contemplated their own beliefs about death, physicians are also better equipped to handle situations in which a patient's wish to die may be explicit. In most circumstances, making certain that the doctor has the capacity to control pain and is not encouraged by external or internal pressures to overtreat is sufficient.

My own experience with dying patients has pointed to a seemingly simple, yet powerful strategy for dealing with death: fostering companionship. Often, just sitting by a patient's side is the best possible medicine for both physician and patient. I have seen how the presence of someone who cares, whether silently or with words, can significantly enhance a patient's well-being, no matter how grave the illness. So, too, can such companionship benefit the clinician.

Once as a young student studying to become a physician, I asked an older physician about his most meaningful experiences in medicine. He replied that he found the most meaning in his role as a physician when he was with dying patients at the time they "turned around to face death." These patients shared with him a most honest and poignant moment, and his companionship, I imagine, enhanced their strength to accept and accommodate themselves to the coming end of their lives. Clinicians who decide that their presence is no longer necessary or useful in the case of terminally ill patients, for whom no treatment options remain, sell both themselves and their patients short.

The experienced clinician realizes that all decisions, both diagnostic and therapeutic, are provisional and subject to revision as time passes and circumstances change. With this realization comes the understanding that the foundation of competent, continuing care is the clinician's commitment to stick with the patient, no matter what turn the course of illness takes. This is not an easy prescription, and the ability to fill it is a hallmark of professional and individual maturity.

Coming in January: Section III—The Broadening Scope of Health Care and Section IV—The Need for a Tenacious Loyalty
. . . plus an afterword and references

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Roberts, David
Rodnick, Jonathan E.
Rodvien, Robert
Rosen, Glenn
Rosenberg, Saul
Ross, Steven E.
Rubin, Geoffrey D.
Ruoss, Stephen J.
Rutherford, George W. III
Salvino, Christopher K.
Salzman, Amy
Sande, Merle A.
Santanello, Nancy
Sarosi, George
Saver, Jeffrey
Schenker, Marc B.
Schillinger, Dean
Senthilselvan
Sergent, John
Shaw, Gary
Shuer, Lawrence M.
Shusterman, Dennis
Singer, Fred
Sloan, Judy
Sonnenberg, Frank A.
Spach, David
Sparks, Robert
Spencer, William
Stamper, Robert
Stolle, Marshall
Sullivan, Robert
Terr, Abba I.
Terris, David J.
Tolle, Susan
Tuhrim, Stan
Turek, Paul
Veves, Aristidis
Volberding, Paul
Wagner, Jr., Franklin C.
Weil, Jon
Weintrub, Peggy Sue
Weisman, Michael
Willett, David
Wilson, Charles B.
Wilson, William C.
Woeber, Kenneth A.
Wu, Albert
Yoshikawa, Aki
Young, Ernle
Young, Lowell
Yuen, Alan R.
Zalopa, Andrew
Zehnder, James
Zimmerman, Leslie H.

Volume 167 INDEX July-December 1997

AUTHOR INDEX

Agger, William A., La Crosse, Wis (July) 40
Albers, Leah, Albuquerque, NM (July) 19
Anderson, Mark, Sacramento, Calif (Aug) 109

Barlow, Cassie B, Wright Patterson AFB, Nev (Aug) 74
Basnyat, Buddha, Kathmandu, Nepal (Sep) 180
Beckham, Sheila, Waianae, Hawaii (Sep) 138
Bertken, Richard D., Fresno, Calif (July) 44
Blackmon, Griffith M., Seattle, Wash (Dec) 387
Blanc, Paul, San Francisco, Calif (Dec) 398
Bonkovsky, Herbert L., Worcester, Mass (July) 50
Brody, Barbara L., La Jolla, Calif (Nov) 336
Brogenicht, Kathryn, San Francisco, Cali (Oct) 291
Buchner, David M., Seattle, Wash (Oct) 258
Bulger, Roger J., Washington, DC (Nov) 362
Burgess, Jefferey L., Seattle, Wash (Dec) 387
Burke, Gregory L., Winston-Salem, NC (Oct) 240

Carlson, Timothy H., Seattle, Wash (July) 10
Carty, Elizabeth, San Francisco, Calif (Oct) 291
Cheung, Ramsey C., Stanford, Calif (July) 23
Cooper, Viraf R., Fresno, Calif (July) 44

Dagogo-Jack, Samuel, St. Louis, Mo (Dec) 435
Derlet, Robert W., Sacramento, Calif (Aug) 109
Detter, James C., Seattle, Wash (July) 10
Donoghue, John, Cleveland Heights, Ohio (Aug) 114
Doucette, Gregory J., Charleston, SC (Nov) 351
Draznin, Boris, Denver, Colo (Sep) 166
Du Clos, Terry W., Albuquerque, NM (Aug) 106

Ellis, Robert J., Ceiba, PR (Dec) 430
Endres, Thomas E., Washington, DC (Oct) 216
Ernst, Amy A., Nashville, Tenn (Aug) 79
Ershler, William B., Baltimore, Md (Oct) 238

Farese, Robert V., San Francisco, Calif (Nov) 353
Feigenbaum, Lawrence Z., San Francisco, Calif (Oct) 291
Fredricks, David N., Stanford, Cali (Nov) 315
Freedman, Marc, Berkeley, Calif (Oct) 216
Fried, Linda P., Baltimore, Md (Oct) 216
(Oct) 240

Gates, George A., Seattle, Wash (Oct) 247
Genovese, Mark C., Stanford, Calif (Sep) 149
Gessner, Bradford D., Anchorage, Alaska (Nov) 351
Goalstone, Marc, Denver, Colo (Sep) 166
Graham, Elinor A., Seattle, Wash (July) 10
Gravenstein, Stefan, Norfolk, Va (Oct) 238
Greenberg, Harry B., Stanford, Calif (July) 23
Grimes, David A., San Francisco, Calif (Sep) 145

Hardee, James T., Albuquerque, NM (Aug) 106
Hazzard, William R., Winston-Salem, NC (Oct) 206
Holman, Halsted R., Palo Alto, Calif (Oct) 265
Horowitz, B. Zane, Sacramento, Calif (Dec) 392
Houry, Debra, New Orleans, La (Aug) 79
Humphry, Joseph, Waianae, Hawaii (Sep) 138

Jacobson, Mark A., San Francisco, Calif (Nov) 315
Jameson, Lolani M., Waianae, Hawaii (Sep) 138
Johnson, Deanna R., Seattle, Wash (Nov) 330

Kalina, Robert E., Seattle, Wash (Oct) 253
Katz, Patricia P., San Francisco, Calif (Dec) 398
Keeffe, Emmet B., Stanford, Calif (July) 23
Khovidhunkit, Weerapan, San Francisco, Calif (Nov) 353
Kirsch, Carl M., San Jose, Calif (July) 47
Kroe, D. Mark, San Jose, Calif (July) 47

La Croix, Andrea Z., Seattle, Wash (Oct) 220
Labbe, Robert F., Seattle, Wash (July) 10
Lai, Lillian P., Pasadena, Calif (Aug) 103
Larson, Eric B., Seattle, Wash (Oct) 203
Learman, Lee A., San Francisco, Calif (Sep) 145
Lenfant, Claude, Bethesda, Md (July) 15
Leveille, Suzanne G., Bethesda, Md (Oct) 220
Litch, James A., Kathmandu, Nepal (Sep) 180
Logsdon, Rebecca G., Seattle, Wash (Oct) 269
Lorig, Kate R., Palo Alto, Calif (Oct) 265
Luce, John M., San Francisco, Calif (Dec) 411

Mancinelli, Laviero, Los Angeles, Calif (Nov) 322
Marinella, Mark A., Dayton, Ohio (Nov) 356
Marvez-Valls, Eduardo, New Orleans, La (Aug) 79
McCurry, Susan M., Seattle, Wash (Oct) 269
McFeeley, Patricia, Albuquerque, NM (July) 19
McNamara, Robert L., Baltimore, Md (Oct) 240
Meston, Cindy M., Seattle, Wash (Oct) 285
Middaugh, John P., Anchorage, Alaska (Nov) 351
Miller, Erik C., Sacramento, Calif (Aug) 109
Mills, Trevor, New Orleans, La (Aug) 79
Minvielle, Lucia, New Orleans, La (Aug) 79
Monane, Mark, Montvale, NJ (Oct) 233
Monane, Susan, Montvale, NJ (Oct) 233
Murakami-Mori, Kaoru, Pasadena, Calif (Aug) 103

Navarro, Lette, Los Angeles, Calif (Nov) 322
Neely, James C., San Francisco, Calif (Aug) 115
Newton, Katherine M., Seattle, Wash (Oct) 220
Nick, Todd G., Jackson, Miss (Aug) 79
Norris, Thomas E., Seattle, Wash (Nov) 330

Rees, Thomas S., Seattle, Wash (Oct) 247
Rizzo, Anne G., Nellis AFB, Nev (Aug) 74
Rojanasthien, Noppamas, Chiang Mai, Thailand (Nov) 315
Roldan, Carlos, A., Albuquerque, NM (Aug) 106

Saint, Sanjay, Seattle, Wash (Dec) 417
Salzmann, Peter, Seattle, Wash (Dec) 417
Schiff, Melissa, Albuquerque, NM (July) 19
Schrier, Stanley L., Stanford, Calif (Aug) 82
Semla, Todd, Evanston, Ill (Oct) 233
Sharma, Om P., Los Angeles, Calif (Nov) 322
Shelton, Andrew A., San Francisco, Calif (Aug) 90
Shulman, Nancy, San Jose, Calif (July) 47
Simon, Harold J., La Jolla, Calif (Nov) 336
Siscovick, David S., Seattle, Wash (Oct) 240
Smith, Charles B., Seattle, Wash (Dec) 420
Sodergren, Katherine K., Seattle, Wash (July) 10
Stadler, Kathleen L., La Jolla, Calif (Nov) 336
Stoller, James, Cleveland, Ohio (Dec) 408
Sullivan, Mark D., Seattle, Wash (Oct) 276
Sweeney, Christopher J., La Crosse, Wis (July) 40

Teri, Linda, Seattle, Wash (Oct) 269
Tong, Myron J., Pasadena, Calif (Aug) 103

Wagner, Edward H., Seattle, Wash (Oct) 295
Wallace, Jeffrey, Seattle, Wash (Oct) 220
Wasik, Barbara, Baltimore, Md (Oct) 216
Wehner, John H., San Jose, Calif (July) 47

Welton, Mark L., San Francisco, Calif . . . . . (Aug) 90
Whorton, Donald, San Mateo, Calif . . . . . (Sep) 159
Wong, Otto, San Mateo, Calif. . . . . (Sep) 159

Zell, Steven C., Reno, Nev . . . . . (Dec) 433
Ziambaras, Konstantinos, St. Louis, Mo . . . . . (Dec) 435
Zimmerman, Leslie, San Francisco, Calif . . . . . (Dec) 440
Zimmerman, Mark, Kathmandu, Nepal. . . . . (Sep) 180

SUBJECT INDEX

A

Aging
auditory . . . . . (Oct) 247
cardiac health and . . . . . (Oct) 240
communities and . . . . . (Oct) 216
community resources for patients. . . . . (Oct) 291
medication use and . . . . . (Oct) 233
. . . . . (Oct) 238
memory and. . . . . (Oct) 269
mobility and . . . . . (Oct) 258
morale and. . . . . (Oct) 276
preventing decline in function, evidence from randomized trials . . . . . (Oct) 295
sexuality and . . . . . (Oct) 285
vision and . . . . . (Oct) 253
women and . . . . . (Oct) 220
AIDS/HIV
AIDS-related histoplasmosis . . . . . (Nov) 315
AIDS-related lymphomas (Alerts, Notices, and Case Reports) . . . . . (July) 40
combination therapy for HIV disease (Epitomes). . . . . (Nov) 346
determining the number of copies of HIV-1 RNA in plasma (Epitomes). . . . . (July) 35
drug reactions in (Epitomes) ... (Nov)344
HIV-associated thrombocytopenia (Alerts, Notices, and Case Reports) . . . . . (Dec) 433
HIV-infected individuals, immunizations in (Epitomes). . . . . (Nov) 343
treatment for HIV infection (Epitomes) . . . . . (Sep) 175
Alaska, need for generalist physicians in . . . . . (Nov) 330
Anesthesia, local, topical lidocaine adrenaline tetracaine versus injectable buffered lidocaine . . . . . (Aug) 79
Antileukotrienes (Epitomes). . . . . (Nov) 345
Asthma
inhaled corticosteroids for (Epitomes) . . . . . (Nov) 348
intramuscular high-dose triamcinolone acetonide in treatment of severe chronic . . . . . (Nov) 322
pulmonary or allergy subspecialty care for adults with. . . . . (Dec) 398
treatment of severe chronic (Editorial). . . . . (Nov) 359

B

Biomedical research, current and future NIH support of . . . . . (July) 15
Bisphosphonates in treatment of osteoporosis (Epitomes). . . . . (Sep) 177
Breast implants, silicone
(Conferences and Reviews) . . . . . (Sep) 149
(Editorial) . . . . . (Sep) 182
scleroderma and (Conferences and Reviews) . . . . (Sep) 159
British Columbia Long-Term Care System . . . . . (Nov) 336

C

Cardiac health, aging and . . . . . (Oct) 240
Children, facial fractures in (Epitomes) . . . . . (Aug) 100
Chlamydia trachomatis, laboratory detection of (Epitomes). . . . . (July) 36
Cocaethylene (Epitomes) . . . . . (July) 38

D

Dementia management, advances in (Epitomes) . . . . . (Sep) 174
Diabetes
management, advances in (Epitomes). . . . . (Sep) 176
social and cultural barriers to care . . . . . (Sep) 138

E

Emergency room, and hazardous material incidents . . (Dec) 387

F

Food poisoning (Correspondence) . . . . . (Sep) 185
Fractures
facial, in children (Epitomes). . . . . (Aug) 100
occult pelvic, magnetic resonance imaging for diagnosis of (Alerts, Notices, and Case Reports) . . . . . (Aug) 109

G

Gerontology, preventive . . . . . (Oct) 206

H

Hazardous material incidents . . . . . (Dec) 387
Hepatic failure, propylthiouracil-induced (Alerts, Notices, and Case Reports) . . . . . (Nov) 353
Hepatitis C virus, development of hepatocellular carcinoma after clearance of (Alerts, Notices, and Case Reports). . . . . (Aug) 103
Hepatitis G virus
(Conferences and Reviews) . . . . . (July) 23
(Editorial) . . . . . (July) 50
Hepatocellular carcinoma, development of after clearance of hepatitis C virus (Alerts, Notices, and Case Reports)(Aug) 103
Histocompatibility complex, diseases associated with (Epitomes). . . . . (July) 36
HIV, *see* AIDS/HIV
Hyperkalemia, trimethoprim-sulfamethoxazole associated with (Alerts, Notices, and Case Reports) . . . . . (Nov) 356
Hypernatremia (Alerts, Notices, and Case Reports) . . (Dec) 430

I

Insulin signaling (Conferences and Reviews) . . . . . (Sep) 166
Iron deficiency, and delayed bottle weaning in southeast Asian toddlers . . . . . (July) 10

K

Kaposi's sarcoma-associated herpesvirus (Epitomes). . . (July) 37

L

Latex allergy (Epitomes) . . . . . (Nov) 344
Life support (Commentary) . . . . . (Dec) 411
Lupus, betaxolol and drug-induced, complicated by pericarditis (Alerts, Notices, and Case Reports. . . . . (Aug) 106
Lymphomas, AIDS-related (Alerts, Notices, and Case Reports) . . . . . (July) 40

M

Mad cow disease (Commentary). . . . . (Dec) 417
Magnetic resonance imaging, for diagnosis of occult pelvic fractures (Alerts, Notices, and Case Reports) . . . . (Aug) 109
Medication use, aging and . . . . . (Oct) 233
. . . . . (Oct) 238
Motor vehicle crashes, and maternal mortality . . . . . (July) 19
Mouth-to-mouth resuscitation, health care professionals' willingness to do . . . . . (Dec) 392

N

Neuromuscular disorders, intravenous immune globulin in (Epitomes). . . . . (Nov) 349
Nocardia braziliensis, anterior mediastinal mass with draining sternal sinus tracts due to (Alerts, Notices, and Case Reports) . . . . . (July) 47

O

Obesity, as chronic disease (Epitomes) . . . . . (Sep) 178
Onychomycosis (Correspondence) . . . . . (July) 52
Osteoarthritis, self-management of . . . . . (Oct) 265

Osteoporosis, bisphosphonates in treatment of (Epitomes) . . . (Sep) 177

P

Pathology
Chlamydia trachomatis, laboratory detection of (Epitomes) . . . (July) 36
cocaethylene (Epitomes) . . . (July) 38
determining number of copies of HIV-1 RNA in plasma (Epitomes) . . . (July) 35
diseases associated with major histocompatibility complex (Epitomes) . . . (July) 36
Kaposi's sarcoma-associated herpesvirus (Epitomes) . . . (July) 37
and patients with heritable thrombotic disorders (Epitomes) . . . (July) 34
Pelvic floor (Conferences and Reviews) . . . (Aug) 90
Pericarditis, as complication of betaxolol and drug-induced lupus (Alerts, Notices, and Case Reports) . . . (Aug) 106
Plastic surgery
computerized CO2 laser resurfacing (Epitomes) . . . (Aug) 100
correction of velopharyngeal insufficiency (Epitomes) . . . (Aug) 101
facial fractures in children (Epitomes) . . . (Aug) 100
microvascular free tissue transfer (Epitomes) . . . (Aug) 99
Pregnancy, ectopic, hospital discharge after . . . (Sep) 145
Pulmonary edema following licorice binge (Correspondence) . . . (Sep) 184

Q

Quest for Mercy, The . . . (Nov) 362
(Dec) 443

R

Respiratory therapist, protocols of (Commentary) . . . (Dec) 408
Rhinitis, pharmacotherapy of (Epitomes) . . . (Nov) 347

S

Scleroderma, and silicone breast implants (Conferences and Reviews) . . . (Sep) 159
Sexuality, aging and . . . (Oct) 285
Shellfish poisoning, (Alerts, Notices, and Case Reports) . . . (Nov) 351
Subarachnoid hemorrhage, at high altitude (Alerts, Notices, and Case Reports) . . . (Sep) 180
Surgical residents, violence against . . . (Aug) 74

T

Thalassemias, pathophysiology of . . . (Aug) 82
Thrombotic disorders, laboratory work-up of patients with (Epitomes) . . . (July) 34

U

Urticaria, treatment of chronic (Epitomes) . . . (Nov) 348

V

VA medical centers, future of (Special Report) . . . (Dec) 420
Vision, aging and . . . (Oct) 253
Vitamin D deficiency, reversible muscle weakness in (Alerts, Notices, and Case Reports) . . . (Dec) 435

W

Wegener granulomatosis (Alerts, Notices, and Case Reports) . . . (July) 44

TITLE INDEX

A

Advances in Allergic Rhinitis Pharmacotherapy (Epitomes) . . . (Nov) 347
Advances in Dementia Management (Epitomes) . . . (Sep) 174
Advances in Diabetes Management (Epitomes) . . . (Sep) 176
Advances in Microvascular Free Tissue Transfer (Epitomes) . . . (Aug) 99
Aging and Sexuality . . . (Oct) 285
AIDS-Related Disseminated Histoplasmosis in San Francisco, California . . . (Nov) 315
AIDS-Related Lymphomas With Neurologic Manifestations (Alerts, Notices, and Case Reports) . . . (July) 40
Alphabet Soup of Viral Hepatitis, The: I G a New Flavi(or) in the Mix? (Editorial) . . . (July) 50
Anterior Mediastinal Mass With Draining Sternal Sinus Tracts Due to *Nocardia braziliensis*, An (Alerts, Notices, and Case Reports) . . . (July) 47
Antileukotrienes—1997 and Beyond (Epitomes) . . . (Nov) 345

B

Betaxolol and Drug-Induced Lupus Complicated by Pericarditis and Large Pericardial Effusion (Alerts, Notices, and Case Reports) . . . (Aug) 106
Bisphosphonates in the Treatment of Osteoporosis (Epitomes) . . . (Sep) 177
Building Communities That Promote Successful Aging . (Oct) 216

C

Closer to Home (or Home Alone?)—The British Columbia Long-Term Care System in Transition . . . (Nov) 336
Cocaethylene: A Novel Cocaine Homolog (Epitomes) . . . (July) 38
Combination Therapy for HIV Disease (Epitomes) . . . (Nov) 346
Community Resources for Frail Older Patients . . . (Oct) 291
Computerized CO2 Laser Resurfacing for Aesthetic Management (Epitomes) . . . (Aug) 100
Correction of Velopharyngeal Insufficiency Using the Furlow Double-Opposing Z-plasty (Epitomes) . . . (Aug) 101
Current and Future NIH Support of Biomedical Research . . . (July) 15

D

Delayed Bottle Weaning and Iron Deficiency in Southeast Asian Toddlers . . . (July) 10
Determining the Number of Copies of HIV-1 RNA in Plasma: Applying This New Test to Management of Patients (Epitomes) . . . (July) 35
Development of Hepatocellular Carcinoma After Clearance of Hepatitis C Virus With Interferon Therapy (Alerts, Notices, and Case Reports) . . . (Aug) 103
Diseases Associated With the Major Histocompatibility Complex (Epitomes) . . . (July) 36
Drug Reactions in HIV/AIDS (Epitomes) . . . (Nov) 344

F

Facial Fractures in Children (Epitomes) . . . (Aug) 100
Fever, Rash, and Arthritis in a Woman With Silicone Gel Breast Implants (Conferences and Reviews) . . . (Sep) 149
Few Words About The Quest for Mercy, A . . . (Nov) 361
. . . (Dec) 442
Final Act, The (Lessons from the Practice) . . . (July) 53
Food Poisoning in Flight (Correspondence) . . . (Sep) 185
Future of VA Medical Centers, The (Special Report) . (Dec) 420

G

Geographic Distribution, Supply, and Need for Generalist Physicians in Alaska . . . (Nov) 330

H

Health Care Professionals' Willingness to Do Mouth-to-Mouth Resuscitation . . . (Dec) 392
Healthy Aging—A Women's Issue . . . (Oct) 220
Hear Ye? Hear Ye! Successful Auditory Aging . . . (Oct) 247
Heart Health in Older Adults—Import of Heart Disease & Opportunities for Maintaining Cardiac Health . . . (Oct) 240
Hepatitis G Virus: Is It a Hepatitis Virus? (Conferences and Reviews) . . . (July) 23
Hospital Preparedness for Hazardous Material Incidents and Treatment of Contaminated Patients . . . (Dec) 387

I

Inhaled Corticosteroids for Asthma Therapy (Epitomes) . . . (Nov) 348
Insulin Signaling (Conferences and Reviews) . . . (Sep) 166
Intramuscular High-dose Triamcinolone Acetonide in the Treatment of Severe Chronic Asthma . . . (Nov) 322
Intravenous Immune Globulin in Neuromuscular Disorders (Epitomes) . . . (Nov) 349

K

Kaposi's Sarcoma-Associated Herpesvirus (KSHV): A New Viral Pathogen Associated with Kaposi's Sarcoma, Primary Effusion Lymphoma, and Multicentric Castleman's Disease (Epitomes) . . . (July) 37

L

Laboratory Detection of *Chlamydia trachomatis* (Epitomes) . . . (July) 36
Laboratory Work-Up of Patients With Heritable Thrombotic Disorders (Epitomes) . . . (July) 34
Latex Allergy—The Latest Insights (Epitomes) . . . (Nov) 344
Long-Term Repression of HIV-Associated Thrombocytopenia Parallels Ongoing Suppression of Viral Replication (Alerts, Notices, and Case Reports) . . . (Dec) 433

M

Mad Cow Disease: An Opportunity for Preventive Medicine? (Commentary) . . . (Dec) 417
Magnetic Resonance Imaging for the Diagnosis of Occult Pelvic Fractures: Two Case Reports (Alerts, Notices, and Case Reports) . . . (Aug) 109
Maintaining Good Morale in Old Age . . . (Oct) 276
Memory, Thinking, and Aging—What We Know About What We Know . . . (Oct) 269
Motor Vehicle Crashes and Maternal Mortality in New Mexico: The Significance of Seat Belt Use . . . (July) 19

O

Obesity as a Chronic Disease (Epitomes) . . . (Sep) 178
Onychomycosis—A Different Perspective (Correspondence) . . . (July) 52
Optimal Medication Use in Elders—Key to Successful Aging . . . (Oct) 233
Overcoming Barriers to Successful Aging—Self-Management of Osteoarthritis . . . (Oct) 265
Overcoming Social and Cultural Barriers to Care for Patients With Diabetes . . . (Sep) 138

P

Paralytic Shellfish Poisoning in Kodiak, Alaska (Alerts, Notices, and Case Reports) . . . (Nov) 351
Pathophysiology of the Thalassemias—The Albion Walter Hewlett Award Presentation . . . (Aug) 82
Pelvic Floor in Health and Disease, The (Conferences and Reviews) . . . (Aug) 90
Physical (Poem) . . . (Aug) 114
Plaintiffs, Defendants, Lawyers, and Lawyers: Facts and Rumors About Silicone (Editorial) . . . (Sep) 182
Preserving Mobility in Older Adults . . . (Oct) 258
Preventing Decline in Function—Evidence from Randomized Trials Around the World . . . (Oct) 295
Pulmonary Edema Following a Licorice Binge (Correspondence) . . . (Sep) 184
Pulmonary and Allergy Subspecialty Care in Adults with Asthma: Treatment, Use of Services, and Health Outcomes . . . (Dec) 398

Q

Quest for Mercy, The—Part I—The Forgotten Ingredient in Health Care Reform . . . (Nov) 362
Part II . . . (Dec) 443

R

Rapid Hospital Discharge Following Laparoscopy for Ectopic Pregnancy—A Promise Unfulfilled? . . . (Sep) 145
Recommendations for Immunizations in HIV-Infected Individuals (Epitomes) . . . (Nov) 343
Resolution of Propylthiouracil-Induced Hepatic Failure After Treatment of Thyrotoxicosis (Alerts, Notices, and Case Reports) . . . (Nov) 353
Respiratory Therapist-Driven Protocols: Rationale and Efficacy (Commentary) . . . (Dec) 408
Reversible Muscle Weakness in Vitamin D Deficiency (Alerts, Notices, and Case Reports) . . . (Dec) 435

S

Scleroderma and Silicone Breast Implants (Conferences and Reviews) . . . (Sep) 159
Seeing Into the Future—Vision and Aging . . . (Oct) 253
Serendipity (Lessons From the Practice) . . . (Aug) 115
Severe Hypernatremia From Sea Water Ingestion During Near-Drowning in a Hurricane (Alerts, Notices, and Case Reports) . . . (Dec) 430
Subarachnoid Hemorrhage at High Altitude (Alerts, Notices, and Case Reports) . . . (Sep) 180
Successful Aging: An Overview . . . (Oct) 204
Successful Aging: Now Is The Time . . . (Oct) 203
Successful Aging Calls for More than Drugs . . . (Oct) 238

T

Topical Lidocaine Adrenaline Tetracaine (LAT Gel) Versus Injectable Buffered Lidocaine for Local Anesthesia in Laceration Repair . . . (Aug) 79
Treatment for Human Immunodeficiency Virus (HIV) Infection (Epitomes) . . . (Sep) 175
Treatment of Chronic Severe Asthma (Editorial) . . . (Nov) 359
Treatment of Chronic Urticaria (Epitomes) . . . (Nov) 348
Trimethoprim-Sulfamethoxazole Associated With Hyperkalemia (Alerts, Notices, and Case Reports) . . . (Nov) 356

V

Violence Against Surgical Residents . . . (Aug) 74

W

Ways to Make "Usual" and "Successful" Aging Synonymous—Preventive Gerontology . . . (Oct) 206
Wegener Granulomatosis Causing Sellar Mass, Hydrocephalus, and Global Pituitary Failure (Alerts, Notices, and Case Reports) . . . (July) 44
Withholding and Withdrawal of Life Support from Critically Ill Patients (Commentary) . . . (Dec) 411

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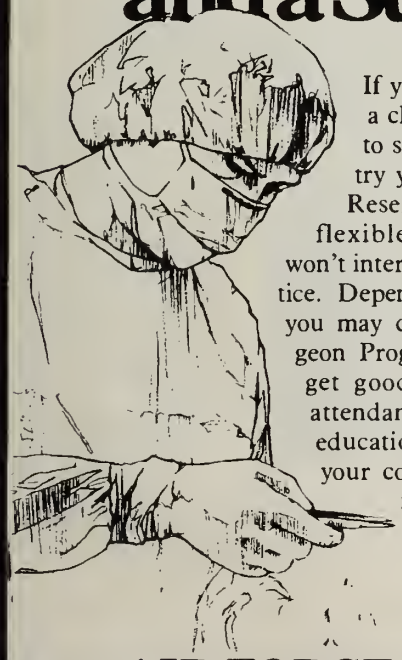

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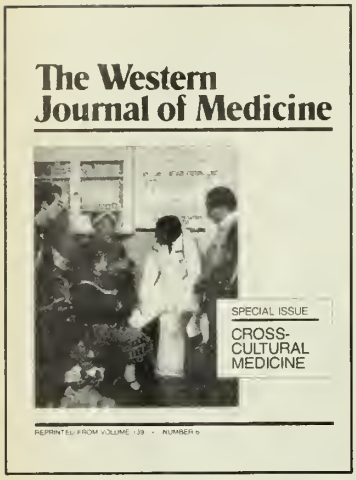

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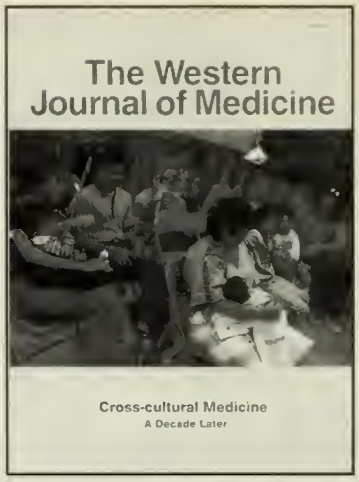

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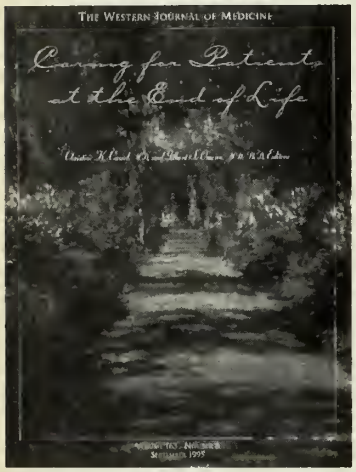

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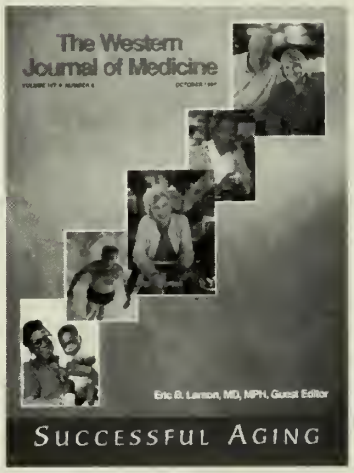

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